Assessment of lung function variability documents postviral asthma in many patients with long covid

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Background: The assumption of this study was that postviral asthma can be detect in patients with long covid (LC). We aimed to evaluate diurnal variability in forced expiratory flow in 1 second (FEV1) over a two-weeks in LC patients with a negative methacholine bronchial provocation test (BPT), and the response of asthma treatment on diurnal FEV1 variability and LC symptoms.

Methods: Referred for easy physical rehabilitation to the Norwegian Sports Medicine Centre in Oslo, Norway, 30 patients with LC for at least six months were included in this study.

Results: Methacholine BPT was deemed positive in 8/30 (27%) patients by an accumulated provocation dose (PD20)<8 µmol causing a 20% fall in FEV1. Diurnal FEV1 variability ≥12% was observed in 21/22 (95%) of the patients with negative methacholine BPT, while one patient dropped out of the study. In the 29 patients with either positive methacholine BPT or excessive lung function variability, three weeks' asthma treatment improved mean FEV1 variability from 18.0% to 7.3%, p<0.001. Significant reduction in perceived burden of LC symptoms were observed on a 10-point Likert scale (0=not troubled, 10=extremely troubled) for fatigue and shortness of breath, from 8.3 to 6.1, p<0.001 and from 3.0 to 0, p<0.001, respectively.

Conclusions: This study indicate that LC patients can benefit from a broad diagnostic evaluation of postviral asthma including diurnal FEV1 variability. Future interventional studies focusing on asthma treatment response in LC patients with evidence of airflow limitation are warranted.

Trends in inhaler use and associated carbon footprint: a sales data-based study in Europe

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Introduction: Physicians are being encouraged to favor dry powder inhalers (DPI) over pressurized metered dose inhalers (pMDI) on environmental grounds. The EU is reviewing the F-gas regulation to accelerate emission cut-down targets.

Objective: Thoughtful use of inhalers can reduce emissions while promoting positive clinical outcomes. We aim to describe the trends of pMDI and DPI use and associated carbon footprint (CF) in Europe.

Methods: DPI and pMDI sales data between 2011–2021 were extracted from IQVIA MIDAS Quarterly 2022, reported as total sold doses in Germany, France, Spain, Italy, Poland, Nordic countries and UK. CF calculations were based on Medical and Chemicals Technical Options Committee 2018 assessment report.

Results: Between 2011 and 2021 CF of inhalation therapy increased from 3.37 Mt to 3.89 Mt CO2e as a result of a 40% increase in the number of sold doses of pMDI and a 10% decrease of DPIs. Replacing pMDIs with DPIs would have produced 92% fewer emissions. In 2021, emissions associated with short acting beta-2 agonists (SABA) were 1.64 Mt CO2e (41% of all emissions), 94% from pMDIs. The UK was the largest source of pMDI-related emissions in 2021 with 1.24 Mt CO2e (31% of all emissions).

Conclusions: CF of inhaler therapy in Europe grew due to an increased use of pMDI and decreased use of DPI in many European countries. Greater focus on guideline-based controller therapy and prioritizing DPIs when clinically appropriate will potentially improve patient outcomes and lower the large greenhouse gas emissions from SABA over-reliance.

Förekomst av och riskfaktorer för ansträngningsutlöst bronkkonstriktion hos unga elitsatsande skidåkare. En screeningstudie med ansträngningstest i köldkammare.

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Bakgrund

Ansträngningsutlöst bronkkonstriktion (EIB) innebär en övergående luftvägsobstruktion i samband med ansträngning och definieras som en minskning med ≥ 10% av den forcerade utandningen under första sekunden (FEV1). EIB är vanligt bland elitskidåkare. Referenstestet för diagnostik är torrluftsprovokation men ansträngningstest (ECT) i fält anses ha högre representativitet och sensitivitet men är svårt att standardisera. ECT i köldkammare kombinerar en idrottspecifik provokation med en standardiserad miljö men har aldrig använts för att undersöka förekomsten av EIB bland vinteridrottare. Målet med studien var att kartlägga prevalensen av EIB hos elitskidåkare med hjälp av ECT i kyla.

Material och metod

De 31 deltagarna (16 kvinnor) var ett slumpmässigt urval av de 174 längdskidåkare och skidskyttar från Sveriges riksidrottsgymnasium och nationella idrottsutbildningar som vintern 2022 deltog i en web-enkät om luftvägssymtom, träning och astma. Sex (19%) deltagare hade använt astmamediciner för en läkardiagnostiserad astma de senaste 12 månaderna. ECT i en köldkammare utfördes (8 min löpning i -14,7 °C, Rh 77% på 85% av beräknad maxpuls) med spirometri före och 5-30 minuter efter.

Resultat

EIB detekterades hos 7 (23%) av deltagarna, 5 av 25 utan astma och 2 av 6 med astma. En deltagare sjönk >15% på FEV1 och hade ingen tidigare känd astma. Kön, ålder, träningstimmar, allergi, FeNO och förekomst av pip/väs från luftvägarna med andnöd de senaste 12 månaderna skiljde sig inte åt mellan deltagarna med och utan EIB.

Slutsats

ECT i kyla påvisar en hög förekomst av EIB hos unga, friska, svenska elitskidåkare, redan tidigt i karriären och oavsett tidigare känd astma. Att förekomsten av EIB hos skidåkarna med astma inte var högre skulle kunna vara ett resultat av deras antiinflammatoriska astmaläkemedel eller överdiagnostik.

Dupilumab Efficacy and Safety in Chronic Obstructive Pulmonary Disease with Type 2 Inflammation

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BACKGROUND: Chronic obstructive pulmonary disease (COPD) is characterized by progressive lung function decline, worsening symptoms, and accelerated by recurrent exacerbations (AECOPD) and evidence of major morbidity and mortality. In some patients, type 2 (T2) inflammation may help drive disease pathogenesis and progression.

METHODS: BOREAS (NCT03930732) was a 52-week (W), phase 3, randomized, double-blind, placebo-controlled trial of efficacy/safety of subcutaneous add-on dupilumab 300mg q2w vs placebo in patients (40–80 years) with moderate-to-severe COPD with T2 inflammation (blood eosinophils ≥300cells/μL) on triple therapy with inhaled corticosteroids (ICS), long-acting β2-agonists (LABA), and long-acting muscarinic antagonists (LAMA) (or LABA/LAMA if ICS was contraindicated).

RESULTS: 939 participants were randomized to placebo/dupilumab (N=471/468). Baseline demographic and disease characteristics were balanced. Dupilumab met all multiplicity-adjusted endpoints. The dupilumab group experienced a 30% reduction in annualized rate of moderate-to-severe exacerbations (p=0.0005) (table 1). Dupilumab significantly increased pre-BD FEV1 at W12 vs placebo (least squares mean (LSM) difference vs placebo: 83mL, p<.0001); sustained through W52 (83mL, p=0.0003). Dupilumab led to statistically significant and clinically meaningful improvement in St. George's Respiratory Questionnaire (SGRQ) at W52 (p=0.0017), proportion of SGRQ responders with improvement 4 points (p=0.0089), and E-RS: COPD RS-Total Score at W52 (p=0.0012). Safety findings were similar and TEAEs were balanced between groups (table 1).

CONCLUSIONS: Dupilumab is the first biologic to significantly improve moderate-severe exacerbations, lung function, health-related quality of life, and symptoms in COPD patients with T2 inflammation. The dupilumab safety profile in patients with COPD is consistent with the safety profile established in other dupilumab indications.

Table 1. Efficacy and Safety Outcomes in the ITT Population

	Difference (95% CI)* for Dupilumab (N=468) vs Placebo (N=471)	P-value
Efficacy: Primary endpoint		
Annualized rate of moderate or severe COPD exacerbation over the 52-week treatment period	0.705 (0.581 to 0.857)	**0.0005**
Efficacy: Key secondary endpoints		
Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo, L	0.083 (0.042 to 0.125)	**<.0001**
Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo, L	0.083 (0.038 to 0.128)	**0.0003**
Safety Treatment-emergent events		
	Placebo (N=470)	**Dupilumab 300 mg q2w (N=469)**
Participants with any TEAE, n (%)	357 (76.0)	363 (77.4)
Participants with any severe TEAE, n (%)	55 (11.7)	48 (10.2)
Participants with any treatment emergent SAE, n (%)	73 (15.5)	64 (13.6)
Participants with any TEAE leading to death, n (%)	8 (1.7)	7 (1.5)
Participants with any TEAE leading to permanent study intervention discontinuation, n (%)	16 (3.4)	14 (3.0)

TEAE – Treatment emergent adverse event; SAE - Serious adverse event

*Difference is relative risk for the primary endpoint and least squares mean difference for key secondary endpoints.

Small airway dysfunction associates with symptoms and emphysema in COPD.

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Background: Small airway dysfunction (SAD) may be a key comorbidity in COPD but its associations with symptoms and emphysema are poorly understood. Impulse oscillometry (IOS) is a forced oscillation technique that is currently used for clinical assessment of SAD in asthma mainly. There is limited understanding of how SAD relates to symptoms and the comorbidity emphysema in COPD.

Aims: To characterise SAD in relation to symptoms and emphysema in a real-life cohort of COPD patients.

Methods: We utilized clinical data from patients with severe COPD who were referred to Karolinska Severe COPD Center for clinical evaluation from 2021 to 23. IOS was performed before dynamic spirometry as a part of the clinical evaluation.

Results: 60 patients (mean age 70.4 years; 54% females) were included. Among these patients, 93% were ever-smokers (mean tobacco load 39.4 packyears), including 20% current and 73% ex-smokers, while 7% were never-smokers. In the medical records, emphysema was reported for 62%, cardiovascular disease for 38% and metabolic disease for 15% of the patients (Table 1). Out of all patients, no less than 83 % had SAD as assessed by IOS. In GOLD stage IV, all patients had SAD.

Both R5-R20 (r=0.308, p=0.018) and AX (r=0.260, p=0.046) displayed a positive correlation with the CAT total score. Multiple regression analysis showed that R5-R20 (R=0.2040, p=0.0152) and AX (R=0.1948, p=0.0189) were also associated with the presence of emphysema.

Conclusion: In patients with COPD, SAD is frequent in all investigated disease stages but it was most frequent in GOLD stage IV. The severity of SAD correlates with symptom score as well as emphysema, indicating that this pathology plays an important role for clinical severity of COPD.

Table 1. Demographics, spirometry and IOS results

	GOLD II n=12	GOLD III n=41	GOLD IV n=7
FEV_1 % of predicted	57.1 (9.3)	39.5 (6.7)	24.8 (4.4)
R_5-R_{20} kPa/l/s#	0.22 (0.38)	0.27 (0.67)	0.35 (0.81)
AX kPa/L#	2.34 (4.12)	3.2 (9.6)	5.26 (11.5)
GOLD Group A (%) B (%) E (%)	 8 (67) 4 (33)	 1 (3) 11 (27) 29 (70)	 3 (43) 4 (57)
CAT score#	25 (22)	22 (28)	25 (18)
Emphysema (%)	4 (33)	29 (71)	4 (57)
Comorbidities Cardiovascular (%) Metabolic (%)	 7 (58) 5 (42)	 14 (44) 4 (10)	 2 (29)

R5-R20: frequency-dependent resistance, AX: area of reactance *mean (SD) #median (range).
IOS values are before bronchodilation.

Feasibility of unsupervised field-based exercise challenge test for diagnosis of lower airway dysfunction

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Background: Digital advancement in healthcare can facilitate diagnosing obstructive respiratory diseases. A portable digital spirometer connected to an app enables unsupervised field-based exercise challenge testing (ECT), and may be superior for detection of lower airway dysfunction (LAD) in athletes compared with laboratory tests. The aim of this study was to evaluate the feasibility of using unsupervised field-based exercise challenge tests for diagnosis of LAD.

Method: This descriptive cross-sectional study examined 60 athletes with current symptoms of LAD, using of unsupervised field-based ECT (AsthmaTuner, Sweden). User-experience and exercise-conditions data were collected through app-registrations and questionnaires. A content analysis was utilised to summarise the qualitative content of questionnaire data.

Results: The athletes included had mean age of 18 years and 40% were female. All athletes completed field-based ECTs under varying ambient conditions in terms of temperature (-11°C to 22°C), weather (cloudy, sunny, indoor, snowing, foggy, windy) and altitude (0-1400 m above sea-level). The information about user-experience indicated that 95% of the athletes found the spirometer and the app easy to use and the implementation of unsupervised field ECTs feasible, while it provided athletes with more knowledge about their respiratory condition. Identified challenges were technical issues with the app and spirometer during cold or windy weather conditions.

Conclusion: Performing unsupervised field-based ECT using a handheld spirometer connected to an app appears feasible for the diagnosis of LAD in athletes.

Type 2 inflammation and cardiometabolic disease

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Background

Asthma has in previous findings been associated with a higher risk for cardiometabolic disease. One possible explanation for this relationship is activation of type 2 inflammation. We aimed to further investigate whether an association can be found between type 2 inflammation and cardiometabolic disease and whether the association varies between different biomarkers.

Methods

A total of 4277 participants with data on cardiometabolic disease (diabetes, cardiovascular disease (CVD), and hypertension) and type 2 inflammation biomarkers (blood eosinophil count, FeNO, and IgE sensitisation) from the Swedish CArdioPulmonary bioImage Study, was included. The presense of type 2 inflammation was defined as blood eosinophils 0.3 x 109/L, FeNO 25 ppb, and/or IgE levels 0.35 PAU/l were considered IgE sensitised. Prevalence of and odds ratio for cardiometabolic disorders were analysed using independent t-test and multivariate logistic regression.

Results

We found a higher prevalence of cardiometabolic disease among participants with any biomarker for type 2 inflammation elevated: diabetes (5.2 % vs 3.3 %, p=0.002), CVD (3.3 % vs 1.8 %, p=0.002) and hypertension (23.7 % vs 20.2 %, p=0.007).

The multivariate logistic regression analysis showed that diabetes had the strongest association to having all three biomarkers elevated (OR 4.03 (95 % CI 1.84-8.87), p=0.001), followed by elevation of both blood eosinophil count and FeNO (OR 2.38 (1.15-4.91), p=0.020) and of only blood eosinophil count (2.02 (1.21-3.36), p=0.007).

CVD was associated with the combination of elevated blood eosinophil count and IgE sensitisation (OR 4.77 (2.11-10.79), p<0.001) and with elevated FeNO (OR 2.57 (1.31-5.06), p=0.006).

Hypertension was associated with elevated blood eosinophil count (OR 1.65 (1.26-2.18, p<0.001).

Conclusion

In conclusion we found an association between type 2 inflammation and cardiometabolic disorder. Further studies are needed to better understand this, but our results strengthen the theory that the pathophysiology of type 2 inflammation and cardiometabolic disease are interlinked.

Proteins associated with preserved ratio impaired spirometry (PRISm)

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Background: Preserved ratio impaired spirometry (PRISm) is a spirometry pattern of interest with regard to incident obstruction and higher mortality. We aimed to apply a proteomic approach to gain more insight into the biological mechanisms associated with PRISm.

Methods: From the population-based Swedish CArdioPulmonary bioImage Study (SCAPIS), participants in Main (n=4,835) and Pilot (n=1,054) studies, were included as discovery and replication cohorts. Lower limit of normal (LLN) for postbronchodilatory FEV1, FVC and FEV1/FVC was defined as 5th percentile in healthy, never-smoking SCAPIS participants. Participants were sub-divided into four groups; Group 0 (reference): FEV1/FVC>LLN & FEV1>LNN & FVC>LLN (n=4,084); Group 1: FEV1/FVC<LLN & FEV1<LLN (n=170); Group 2: FEV1/FVC<LLN & FEV1>LLN (n=278) and Group 3 (PRISm): FEV1/FVC>=LLN & FEV1<LLN (n=238). Restrictive spirometric pattern (RSP) was defined as FEV1/FVC ≥LLN & FVC<LLN (n=238). Proximity extension assays were used to measure 168 proteins. Then the associations of each standardized protein were assessed with each study group by multiple linear regression models, adjusting for age, sex, BMI, smoking, physical activity, study centers, and corrected for multiple testing to control for false discovery rate under level 5%.

Results: Eight proteins that were associated with PRISm could be replicated: Tumor necrosis factor receptor superfamily member 10A, Interleukin -6 (IL-6), S-paraoxonase, Renin, urokinase plasminogen activator surface receptor (U-PAR), E-selectin , Matrix metalloproteinase-7 and Chitinase -3-like protein 1. IL-6 and U-PAR were also associated with Group 1 and SELE with RSP. In addition, 6 other proteins were associated with Group 1 and 3 with RSP. No proteins were associated with group 2.

Conclusion: The protein profile in PRISm differed from both chronic airflow limitation and RSP suggesting specific disease mechanisms.