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Editorial

Personalization of Device Therapy – Prime Time for Peak Inspiratory Flow Rate

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; National Health and Nutrition Examination Survey, **NHANES**; Global initiative for chronic Obstructive Pulmonary Disease, **GOLD**; metered dose inhalers, **MDIs**; dry powder inhalers, **DPIs**; tumor necrosis factor α, **TNFα**; forced vital capacity, **FVC**; forced expiratory volume in 1 second, **FEV_1**

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Chronic obstructive pulmonary disease (COPD) is expected to be the third leading cause of death worldwide by 2030.[1] Readmissions are highly prevalent[2] and costly. In 2013, the Healthcare Cost and Utilization Project[3] recorded 114,067 readmissions for COPD in the United States, a 20% readmission rate which cost payers $1.38 billion, not accounting for morbidity and lost productivity. Readmissions can be influenced by many factors including disease severity, comorbidities, socioeconomic issues, variable pharmacological and nonpharmacological adherence.[4]

Comorbidities are highly prevalent in COPD.[5] A multi-year National Health and Nutrition Examination Survey (NHANES) of individuals aged more than 45 years found that individuals with COPD were more likely than those without COPD to have coexisting arthritis (54.6% versus 36.9%), depression (20.6% versus 12.5%), stroke (8.9% versus 4.6%), polypharmacy with use of >4 prescription medications (51.8% versus 32.1%), memory problems (18.5% versus 8.8%) and visual impairment (14.0% versus 9.6%).[6] These comorbidities impact the timely delivery of the prescribed dose of inhaled medications, which require manual dexterity and coordination with the inhaled device for optimal particle delivery.

According to the new Global initiative for chronic Obstructive Lung Disease (GOLD) 2017 guidelines,[7] "the choice of inhaler device has to be individually tailored and will depend on access, cost, prescriber, and most importantly the patient's ability and preference." Therefore, personalization of inhaler selection goes beyond pharmacologic drug selection to involve the crucial step of device selection that requires assessment of patient coordination and potentially peak inspiratory flow rate.

Metered dose inhalers (MDIs) are commonly prescribed for patients with airway diseases such as COPD and asthma, but MDIs are difficult to use for patients with coordination issues and handling problems.[8] A wide range of dry powder inhalers (DPIs) exist, and each DPI carries an intrinsic resistance requiring minimum inhalation flows that is not inherent in MDIs. In a systematic review across 40 years, Sanchis et al compared errors in inhaler steps for DPIs and MDIs, and found that DPIs have lower handling problems compared to MDIs.[9]

For a DPI, an adequate inspiratory effort is crucial to cause the pressure drop[10,11] that promotes disaggregation of particles within the inhaler into fine particles. For optimum deposition into the lower respiratory airways, particles should be aerodynamic dynamic at less than 5 micrometers. Therefore, for

DPIs, patients are instructed to take a "deep and fast" inhalation, while for MDIs, they are encouraged to take a "slow and deep" inhalation to avoid excessive oropharyngeal deposition which can arise if they use the DPI inhalation method.

However, respiratory muscle function is often compromised in COPD exacerbations, due to hyperinflation, hypoxemia and muscle wasting. Lung hyperinflation leads to shortening of diaphragm muscle fibers and alteration of fiber type,[12] causing functional weakening.[12] Ageing, arthritis or kyphoscoliosis, and malnutrition[13] lead to reduced respiratory muscle strength that decreases PIFRs.[14,15,16] In stable patients with severe COPD, inspiratory muscle strength is significantly less than expiratory muscle strength.[17] Systemic inflammation plays a key role in skeletal muscle dysfunction.[18] Increased work of breathing significantly upregulates inflammatory cytokines interleukin-6, interleukin-1 beta and tumor necrosis factor α (TNFα),[19] while TNFα is also increased in relation to hypoxemia.[20]

A quick and convenient measure of a patients' maximal inspiratory pressure can be obtained with a commercially available device (InCheck™ DIAL, Alliance Tech, Texas). This has been calibrated using an American Thoracic Society pulmonary waveform generator, and complies with the Australian/New Zealand standard for back pressure in flow meters. By rotating a dial to the desired DPI, it simulates the intrinsic resistance of that selected inhaler.[21]

While a PIFR >30 L/min has generally been the minimal PIFR,[22,23] a PIFR >60 L/min against the internal resistance of the particular DPI is considered optimal to inhale the dry powder inhaler.[24,25] In vitro, cascade impaction studies such as those conducted by Feddah et al[26] determine the influence of inspiratory flow rate on the fine particle mass which gets deposited in the lungs. By increasing the inspiratory flow rate from 30 L/min to 60 L/min to 90 L/min, fine particle mass is significantly increased by 17% and 75% for the Flixotide Accuhaler (DISKUS®), and by 1.2 and 2.2- fold for Pulmicort Turbuhaler®. Increased flow rates generate higher fine particle fraction.[27,28]

Suboptimal inspiratory flow rates are an under recognized problem. In elderly, stable outpatients with severe COPD, Mahler et al[29] found the prevalence of PIFR < 60 L/min against the diskus was 19%, while Janssens et al[14] found that 30% had a PIFR < 45 L/min against the turbuhaler. During an acute exacerbation, the prevalence of suboptimal PIF can be as high as 52%,[30] or 32% following hospitalization for COPD exacerbation.[31]

Suboptimal PIFR was found to be associated with age, inspiratory capacity, female gender, shorter height and lower forced vital capacity (FVC) in stable outpatients with severe COPD.[25] Age and gender were more important determinants of PIFR than the degree of airway obstruction.[32] Most importantly forced expiratory volume in 1 second (FEV_1) (percent predicted) has not been found to be associated with PIFR.[14,32] Janssens et al[14] found that in terms of pulmonary function test parameters, PIFR measured by the InCheck™ DIAL method correlated with PIFR derived from spirometry (r=0.51), FVC (r=0.46) and maximal inspiratory pressure (r=0.42) in stable outpatients. Their subsequent stepwise multiple regression analysis found that spirometric PIFR was the only independent predictor for explaining the variance of PIF at any resistance (Aeroliser: R^2=0.45, p<0.001; DISKUS®: R^2=0.42, p<0.0001; Turbuhaler: R^2=0.39, p<0.001).

How about situations where the InCheck™ DIAL is not available? Seheult et al[33] assessed the correlation of spirometric PIFR with DISKUS® PIFR in healthy volunteers and patients with asthma, COPD, neuromuscular disease and non-respiratory disorders. When the DISKUS® PIFR threshold was 60 L/min (the "optimal" PIFR threshold), 84% of patients were correctly classified above or below this threshold by using a spirometric PIFR cutoff of 196 L/min. This spirometric PIFR cutoff of 196 L/min may be useful in outpatient clinics without the InCheck™ DIAL as it screens for those patients who are not suitable for DISKUS® DPI. However, we need to understand the limitations of using spirometric PIFR for all patients because it is performed without the resistance that differs among the various DPI and only moderate correlation was found with the DISKUS® PIFR (adjusted R^2 = 0.58, p< 0.0001). A spirometric PIFR cutoff of 196 L/min will still incorrectly classify 14% of patients as DISKUS® optimal or suboptimal. Therefore, checking PIFR against the particular DPI resistance is still advised to ensure adequate flows when using DPIs.

Another commercially available device is the Vitalograph AIM™ (Aerosol Inhalation Monitor).[34] This is a device used to train patients to use their inhalers properly, via an attachment to an MDI or DPI inhaler simulator mouthpiece. Unlike the InCheck™ Dial, this analyses patient inhaler technique at different stages -

from inspiratory acceleration at the start of inspiration, timing of firing of MDI inhaler simulator, inspiratory flow rate throughout inspiration, inhalation time within target flow range and breath hold time at the end of inhalation.

In this issue of the Journal, Sharma and colleagues[31] demonstrated in a prospective multicenter observational study the prevalence of low PIFR (PIFR <60 L/min) within 24 hours of discharge from a COPD-related hospitalization, and analyzed treatment patterns and rehospitalizations by PIFR. They found that after hospitalization for COPD exacerbation, low PIFR prior to discharge is common, affecting 1 in 3 patients. Overall, patients had severe airflow obstruction, with high symptom burden as determined by COPD Assessment Tests and modified Medical Research Council scores. Patients with low PIFR were older, more likely to be female, and also, to be current smokers. Pneumonia (38.8% versus 22.4%, p=0.020) and ischemic heart disease (14.1% versus 3.5%, p=0.015) were more common in the low PIFR cohort. Nearly 70% of patients in the low PIFR cohort received DPI devices at discharge without a significant increase in readmission rate.

The work of Sharma and colleagues[31] is similar to our recent observational study assessing the clinical impact of suboptimal PIFR where patients admitted for COPD exacerbation were enrolled in a respiratory therapist managed pathway. In this study, the prevalence of a suboptimal PIFR was quite high at 52% versus 33%. Contrary to the Sharma study, we found that patients with suboptimal inspiratory flow rates were found to have increased rates of COPD readmission, as well as fewer days to COPD readmission compared to those with optimal PIFR.[30] However, patients with suboptimal PIF discharged on nebulized bronchodilators, had more days to readmission compared to those using DPI.[30] The likely cause for the discrepancy between these 2 studies is that the Sharma study was underpowered to detect differences between the optimal and suboptimal PIFR groups for all cause readmissions following the index hospitalization. In support of our observations, Mahler et al showed in a single-blind, randomized crossover study, that in patients aged more than 60 years with COPD and suboptimal PIFR (<60 L/min), nebulized arformoterol had greater volume responses measured by FVC and inspiratory capacity at 2 hours compared to patients on diskus DPI. Although FEV_1 was significantly better for arformoterol compared to salmeterol at the 15min and 30min time points, there was no significant difference at 2 hours.[35] Studies in asthma patients found that low PIFR also tended to be associated with poor asthma control among the higher resistance Turbuhaler compared to Accuhaler (Diskus) users in patients given DPI with inhaled corticosteroids.[36]

While prescribing inhalers based on pharmacology for different GOLD groups has been well described in GOLD guidelines,[7] there are no current guidelines in terms of prescribing inhaler device types for asthma or COPD. The characterization and severity of airflow obstruction is based on expiratory flows, but the importance of inspiratory flows should not be neglected.

We recommend that PIFR should be directly measured against the resistance of the respective inhalers. This is important for several reasons. First, to assure that the patient has received the optimal dose of medication delivered from the inhaler, without which expected benefits will not be achieved. Second, for prognostication because it determines how well a patient is able to receive inhaled therapies for local effect on diseased airways, and provides an assessment of readmission risk. Third, COPD readmissions have a huge socioeconomic burden and there are limited interventions to prevent them. This is an easy step to modify prescribed inhaler therapies which may greatly benefit at risk patients. Lastly, in this age of personalized medicine, inhaler device heterogeneity provides patients with a wide selection of devices to tailor to their preference, comorbidities and lifestyle. Therefore, assessing PIFR is a key step in device selection to optimize fine particle deposition in the airways.

From the growth of evidence on the importance of PIFR, it is prime time to include PIFR in our assessment of COPD patients. Incorporating measurement of PIFR is quick, simple and convenient to perform at bedside or in the clinic. This is especially important in the elderly, females and those with short stature.[25] The lack of correlation of PIFR with FEV_1[14,32] means that PIFR should be measured regardless of FEV_1. We recommend performing PIFR prior to discharge for patients admitted for COPD exacerbation, and also, routinely during clinic visits to ensure optimum device selection and drug delivery. In patients with suboptimal PIFR, alternative delivery devices such as flow independent aerosol delivery systems, soft mist inhalers, MDI with spacers or jet nebulizers should be considered.

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