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Standardized inhalation capability assessment: A key to optimal inhaler selection for inhalation therapy

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Inhalation therapy has become one of the fundamental treatments for chronic obstructive pulmonary disease (COPD) and bronchial asthma (asthma).[1,2] Meanwhile, with the development of inhaled formulations and devices, inhalation therapy has shown a wide prospect of expanding indications, including respiratory diseases such as lower respiratory tract infections,[3] interstitial lung diseases, lung cancer,[4] as well as other diseases such as diabetes and depression.[5] Compared to oral and intravenous administration, the aerosolized drug is inhaled and acts directly on the airways and lungs, which has the advantages of rapid onset, sustained efficacy, and low systemic adverse effects.[6] Compared to the nebulizer, the hand-held inhaler is a better option for out-of-hospital drug delivery because the latter is easier to operate, requires shorter inhalation time, and has less environment extravasation.[6]

The commonly used inhalers include pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs). The general requirements for using inhalers are to exhale deeply and slowly before inhaling, as well as to hold the breath preferably for about 10 s and then exhale slowly after inhalation. Also, different inhalers require specifically peak inspiratory flow against inhalers' internal resistance (PIFr), inspiratory pattern, and actuation–inhalation coordination (Table 1).[6–10] It was reported that the error rates of different devices ranged from 58.9% to 87.9%, while suboptimal PIFr was common in patients with asthma or COPD.[11–15] Critical errors in inhaler use, including lack of synchronization, expiration in powder device before inhalation, and remaining powder in the capsule by the end were associated with an increased rate of severe COPD exacerbation.[16] Also, a systematic review identified an association between inhaler errors and poor asthma control, COPD disease stability, and greater economic burden on health.[17] Inspiratory flow rates failing to meet inhaler requirements, incorrect inspiratory patterns, or uncoordinated maneuvers would lead to insufficient drug deposition at the targeted position and inadequate drug efficacy, which in turn would increase the risk of acute exacerbation of diseases, hospitalization, emergency room visits, and economic burden.[17,18]

Therefore, health-care providers should assess the patient's inhaler technique accurately and select a proper inhaler accordingly. However, the assessment process is now mostly based on personal clinical experience, is nonhomogeneous, and lacks objective measurements. Based on the available clinical studies and pharmacological studies, we hereby propose a tentative structured assessment of inhalation capability for clinical practice and further studies. The assessment should contain patient's inhalation maneuver (including actuation-inhalation synchronization), PIFr, and breath-holding time. The evaluation of inhalation maneuver and breath-holding time can be accomplished by clinical observation, while PIFr may require an objective quantitative measurement following a standardized procedure, besides clinical observation.

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Table 1: Requirements of inspiratory flow and maneuver for using inhalers[6–10]

Inhalers		Internal resistance levels	Minimal PIFr (L/min)	Optimal PIFr (L/min)	Inhalation maneuvers
pMDIs	Traditional pMDI, Aerosphere®	Nearly no resistance	10	30	Inhale slowly, steadily, and deeply, synchronously actuating the inhaler after initiating inspiration
SMIs	Respimat®	No resistance	10	30	Actuate the inhaler and simultaneously inhale slowly, steadily, and deeply
DPIs	Breezhaler®	Low resistance	20–50	30–65	Inhale forcefully through the mouth from the very beginning until the lungs are full
	Accuhaler®/Diskus®, Ellipta®	Medium-low resistance			
	Turbuhaler® (combination)	Medium resistance			
	Turbuhaler® (monotherapy), Easyhaler® C (combination)	Medium-high resistance			
	HandiHaler®, Easyhaler® M (monotherapy)	High resistance			

PIFr: peak inspiratory flow against resistance; pMDIs: pressurized metered-dose inhalers; SMIs: soft mist inhalers; DPIs: dry powder inhalers.

PIFr is the most important indicator of the evaluation of inhalation capability for DPIs. Clinical evidence showed that inhaling drugs with too low PIFr (< 30 L/min) could not relieve bronchospasm during an asthma attack in patients.[19] When PIFr increased from lower levels to near-optimal levels, the lung deposition rate of drugs inhaled via DPIs increased significantly.[20] However, excess inspiratory flow rates could lead to negative effects, including increased drug deposition in the central airways and decreased drug deposition in the peripheral airways.[21] The increased oropharyngeal drug deposition might lead to hoarseness and other adverse reactions. It was shown that PIFr-guided inhalation therapy (including PIFr assessment and inhaler use training) had an independent correlation with reduced risk of severe acute exacerbation of COPD.[22] Patients with suboptimal PIFr (≤ 60 L/min) had higher rates of readmission for COPD within 90 days, higher rates of all-cause readmissions, and shorter intervals of readmission caused by COPD.[23,24] The COPD patient's PIFr at discharge could also predict all-cause readmissions within 30 and 90 days.[25] This might be related to the patient's poor inhalation capability failing to fully exploit the drug's efficacy in DPIs.

The clinical observation for the evaluation of PIFr includes inspiratory muscle strength and disease condition. The maximal inspiratory pressure is positively correlated with PIFr,[26] which is generated by the respiratory muscle strength and tone.[27] Age and gender were independently associated with PIFr partly by influencing inspiratory muscle strength.[27–29] The frailty could affect the inspiratory muscle strength and the maximum inspiratory pressure, thus decreasing PIFr.[30] People with COPD and asthma tended to have lower PIFr than healthy people.[15,31] Also, participants with active asthma or COPD exacerbation showed a lower PIFr than those without an exacerbation.[7] Individuals with suboptimal PIFr were common among COPD patients hospitalized for acute exacerbations.[23,32] Age, female sex, weak inspiratory muscle strength, frailty, pulmonary diseases such as COPD and asthma, and acute exacerbation are related to low inspiratory flow rates and failure to achieve optimal PIFr. If the patient is in these conditions, health-care providers should consider selecting an inhaler with a relatively lower requirement for inspiratory effort, and measuring PIFr objectively would ensure an optimal inhaler prescription.

The ideal device for PIFr measurement should be portable, easy to operate, user-friendly, affordable, and with a good accuracy and repeatability. In-Check DIAL™ G16 (Clement Clarke International, Harlow, UK and Alliance Tech Medical), a hand-held flow meter specifically designed to measure PIFr, is mostly widely used in clinical research and practice abroad. In-Check DIAL simulates the resistance of different inhalers by adjusting the resistance aperture, with a measurement range of 15–120 L/min and an accuracy of ± 10% or ± 10 L/min (whichever is greater).[33,34] It is portable, inexpensive, and simple to operate, making it suitable for the detection of PIFr both in the hospital and at home. It has been proved that In-Check DIAL can help to guide inhaler choice and improve patients' PIFr performance.[32]

Supposedly, a novel flow sensor–based spirometer, PF810® (UBREATH, Hangzhou, China) can simulate different levels of resistance, similar to In-Check DIAL, by stepper motors.[35] It uses the flow sensor to quantitatively detect PIFr and the flow waveforms during the user's inhalation. PIFr, inspiratory time, inspiratory volume, and breath-holding time are analyzed by computer programs. However, its efficacy for clinical use needs to be validated. Moreover, it needs environmental calibration and is less portable and more expensive than In-Check Dial. Therefore, it is more suitable for use in hospitals. It should be noted that routine spirometers are not suitable for PIFr measurement due to the minimal resistance.

Accurate and reliable measurement of PIFr is dependent on the correct testing procedure. For evaluating the inhalation capability of DPI, the patient should follow the following steps: (1) sit or stand up straight and tilt head; (2) exhale slowly and as completely as possible; (3) place the mouthpiece between the lips and ensure no air leakage; (4) inhale deeply and quickly and keep the inhalation as steady as possible; (5) hold the breath about 10 s and then exhale slowly; and (6) repeat the above procedures for three times and take the maximum value to determine whether the minimum and optimal PIFr of the inhaler can be reached.[27] Incomplete exhalation at step 3 or failure to inhale deeply, rapidly, and forcefully at step 4 would lead to an underestimation of PIFr.

For instruments with calibration requirements, BTPS calibration should be performed each time the device is turned on and it should be recalibrated when the environmental conditions change greatly. Otherwise, measurement errors might happen. Extreme environments might affect not only the device, but also the patient's inhalation capability. For example, high altitude conditions would lead to decreased inspiratory muscle strength,[36] which in turn affects the inhalation capability.

In addition to PIFr, the inspiratory pressure, inspiratory time, and inspiratory volume during inhalation could also reflect the inhalation performance. Theoretically, the inspiratory time and volume can be useful parameters to assess the inspiratory pattern, especially as dose emission varies in different inhalers. However, the study of these indicators in the guidance of clinical medication is still lacking, and their clinical correlation with drug efficacy has yet to be confirmed by further studies.

In conclusion, the assessment of inhalation capability should be performed in a structured and standardized way to guide inhaler prescriptions, combining clinical observation and objective measurements of inhalation maneuvers, PIFr, inspiratory volume, inspiratory time, and breath-holding time. The assessment would help to accurately determine whether the patient is able to use a specific inhaler with sufficient efficacy. For example, PIFr assessment would help to tell whether the patient can achieve the optimal PIFr of DPIs, and actuation–inhalation coordination evaluation would indicate whether the patient is capable of operating pMDIs. Further in-depth research will help optimize inhalation therapy strategies and improve the effectiveness of inhalation therapy.

Conflict of Interest

None declared.

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