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PRACTICAL APPLICATION

# Demystifying Dry Powder Inhaler Resistance with Relevance to Optimal Patient Care

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## Abstract

The selection of an inhaler device is a key component of respiratory disease management. However, there is a lack of clarity surrounding inhaler resistance and how it impacts inhaler selection. The most common inhaler types are dry powder inhalers (DPIs) that have internal resistance and pressurised metered dose inhalers (pMDIs) that use propellants to deliver the drug dose to the airways. Inhaler resistance varies across the DPIs available on the market, depending largely on the design geometry of the device but also partially on formulation parameters. Factors influencing inhaler choice include measures such as flow rate or pressure drop as well as inhaler technique and patient preference, both of which can lead to improved adherence and outcomes. For optimal disease outcomes, device selection should be individualised, inhaler technique optimised and patient preference considered. By addressing the common clinically relevant questions, this paper aims to demystify how DPI resistance should guide the selection of the right device for the right patient.

## Plain Language Summary

Selection of the right inhaler is important to ensure that patients with respiratory diseases get the most benefit from their treatment. Dry powder inhalers and pressurised metered dose inhalers are the most common inhaler types. Pressurised metered dose inhalers use propellants to deliver the drug to the lungs. In contrast, dry powder inhalers deliver the drug to the lungs by having internal resistance. This restricts the flow of air through the inhaler. As the patient inhales through the inhaler, the resistance against the air flow generates the power to separate the drug molecules and carry them to the lungs. While there are many factors to be considered for inhaler selection, there is often confusion around how resistance should guide selection of inhaler. With low-resistance devices, patients must inhale faster to generate the power to separate the drug molecules, which may be difficult in patients with poor lung function. With high-resistance devices, patients do not need to inhale as fast to separate the drug, and most patients can effectively use the inhaler. This article addresses the common clinically relevant questions to clarify how the internal resistance of the inhaler should be used to help guide the selection of the right device for the right patient.

## 1 Introduction

Inhaler devices are a key component of asthma and chronic obstructive pulmonary disease (COPD) treatment, but selecting the right device for the right patient can create challenges for the healthcare professional (HCP) and the patient. Pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) are two of the most common inhaler device types. pMDIs have negligible airflow resistance and use propellants to deliver the drug into the lungs. In contrast, DPIs have much higher airflow resistance and require energy from the patient to successfully deagglomerate the active molecules and deliver them to the lungs [1, 2]. This paper aims to explore the variation in airflow resistances of different DPIs available on the market, with the aim of supporting the selection of the right device for the right patient.

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**Key Points**

Assessing and choosing the right device for the right patient is the first step to successful inhaler use; incorrect choice is likely to be associated with worsened patient outcomes and increased healthcare utilisation.

Differential pressure is created by the inspiratory flow through the inhaler against its internal resistance. With low-resistance devices, patients must create a higher inhalation flow rate to produce the differential pressure required to deagglomerate the active molecules, while with high-resistance devices a lower inhalation flow rate would be sufficient.

With low-resistance devices, the resistance of a patient's lungs limits the peak flow rate achievable during inhalation. Therefore, patients with compromised lung function may not be able to achieve a sufficient flow rate through a low-resistance inhaler to generate adequate differential pressure for optimal drug delivery. With high-resistance devices, most patients can generate a sufficient pressure drop across the device to achieve effective performance.

## 2 Clinically Relevant Questions

### 2.1 What Factors Should be Considered when Choosing the Right Device for the Right Patient?

A variety of factors should be considered when choosing the right device for the right patient: age, frailty, disease control, inhaler technique, inspiratory capacity, patient ability/dexterity, the likelihood of patient adherence to treatment and the patient's own device preference [1, 3]. Several algorithms provide support in identifying the right device for the right patient. A good example is the Access Choose Train (ACT) algorithm [4].

Correct inhaler technique is necessary for successful drug delivery to the lungs and peripheral airways [3]. Therefore, the patient's ability to implement the correct technique must be an important consideration in device choice. For example, DPIs that use a capsule require good dexterity, eyesight and hearing ability. While all DPIs are breath actuated, some DPIs have a breath-actuated mechanism (BAM) requiring the patient to create sufficient pressure drop to release dose efficiently during inhalation. For DPIs without a BAM, the patient must create a fast enough ramp-up rate in their inspiratory manoeuvre to achieve optimal drug deagglomeration [5]. Other factors worth considering are device cost and availability, the presence of dose indicator, availability of formulary and environmental impact [1, 4].

Choosing the right device for the right patient is the first step to successful inhaler use; incorrect choice is likely to be associated with worsened patient outcomes and increased healthcare utilisation [6].

### 2.2 What is Inhaler Resistance, Why Do DPIs have Resistance, and Do all DPIs have the Same Resistance?

Inhaler resistance is the internal airflow resistance of the device, which restricts the flow rate of the air through it (Fig. 1) [7]. As DPIs are breath activated, they require users to inhale forcefully against the internal resistance of the inhaler device to create the internal differential pressure and generate the power required to deagglomerate the drug powder into fine particles that will penetrate the peripheral airways [1, 8, 9]. Not all DPIs have the same degree of resistance; it can vary depending upon the design elements of the device and the specific drug formulation [7, 8, 10]. Figure 1 shows the impact of resistance of DPIs on differential pressure and airflow. As power is the product of flow rate and differential pressure, inhalers must have some airflow and some differential pressure for there to be some power in the airflow through them; provided the resistance is higher than zero and lower than infinity, patients can create a differential pressure across the DPI upon inspiration, and some of this inspiratory power can be harnessed to deagglomerate and aerosolise the drug powder. As the relationship between airflow and power is not linear, the peak of inspiratory power occurs substantially below maximum airflow; high airflow is not necessary to generate sufficient power and is therefore achievable by different patient populations (Fig. 2A).

The term 'high resistance' often causes confusion as the clinical relevance is not immediately obvious. Contrary to what might be considered the natural assumption, high resistance is not a disadvantage for patients—DPIs with medium or high resistance require lower inspiratory effort to transport the drug molecules to the lungs [10]. As the pressure required to deagglomerate the active molecules into fine particles is directly related to the internal resistance of the inhaler device and the inspiratory airflow rate, low resistance devices—despite feeling easy to inhale through—require a higher inspiratory airflow rate and effort, which often cannot be achieved by patients with compromised lungs [7]. In contrast, in high-resistance devices the inspiratory airflow rate is less important for drug deagglomeration than the differential pressure (the difference between

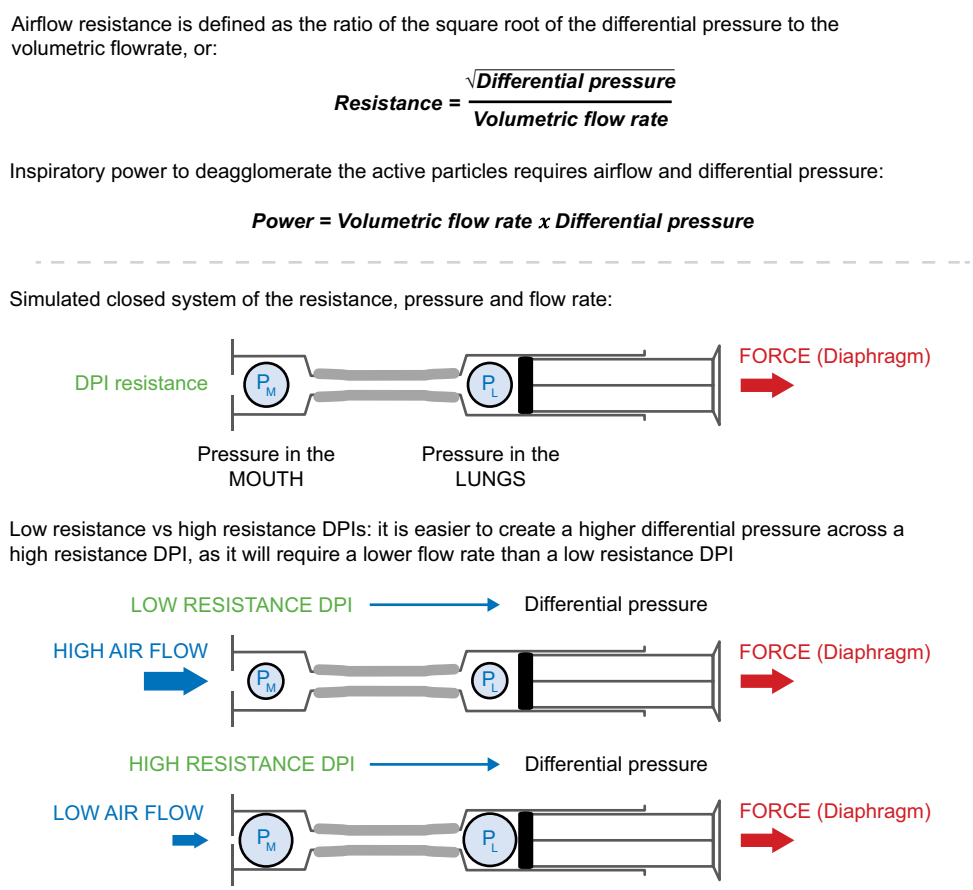


**Fig. 1** Impact of high versus low dry powder inhaler (DPI) resistance on differential pressure. DPI resistance ($\sqrt{Pa}$ min $L^{-1}$) is defined as the ratio of the square root of the differential pressure (Pa) across it to the flow rate through it.

atmospheric and mouth pressure). Consequently, patients can generate a higher differential pressure with a lower inspiratory airflow and less effort [7]. The patient's inspiratory flow rate also impacts drug air velocity within the oropharynx, upper airways, and lung bronchioles; velocity will be lower when inhaling through a high-resistance device due to limited maximum inspiratory flow rate. Lower airflow velocities produce lower drug particle inertia; the particles can, therefore, penetrate deeper into the lung, leading to greater therapeutic effect [8, 11].

High-resistance devices are effective across different patient populations. As inhaler resistance decreases, people with greater maximal inspiratory capacity (e.g. healthy adults) can achieve greater airflow than people with lower capacity (e.g. children and patients with COPD) (Fig. 2). Therefore, dosing is more consistent across different patient groups when using high-resistance devices compared with low-resistance devices [9, 11].

## 2.3 Is it Possible for Patients to Breathe too Quickly and Deeply for a DPI?

While achieving the correct inspiratory flow is necessary for effective pMDI use, for DPIs, it is more important that patients maintain an initial inspiratory flow exceeding a minimum value [1, 2, 9]; due to the inherent resistance, it is almost impossible to inhale too fast through most DPIs. All inhaler users will achieve a lower flow rate and higher pressure drop across the device when inhaling through a higher-resistance DPI. The higher the pressure drop, the greater the ability to deagglomerate and aerosolise the dry powder and for the fine particle fraction to reach the lungs [11].

In clinical practice, some patients inhale at a very high flow rate, especially when inhaling through low-resistance DPIs. Whether high flow rate is associated with adverse events is not clear, as trials do not report absolute flow rate; in clinical practice, it does not appear to pose a challenge.

## 2.4 What is Peak Inspiratory Flow Rate (PIFR), and What Role Should it Play in the Choice of Inhaler Device?

PIFR is the maximal flow rate achieved during an inspiratory manoeuvre, typically expressed in L/min. PIFR is measured in the absence of resistance during lung function testing [9]. While useful, PIFR is a proxy measure and might be measured incorrectly in clinical practice. Therefore, it should not be used in isolation. The controlling parameter for DPIs is not PIFR, but the speed at which PIFR is achieved (i.e. the speed of the initial inspiratory effort). Therefore, for DPIs it

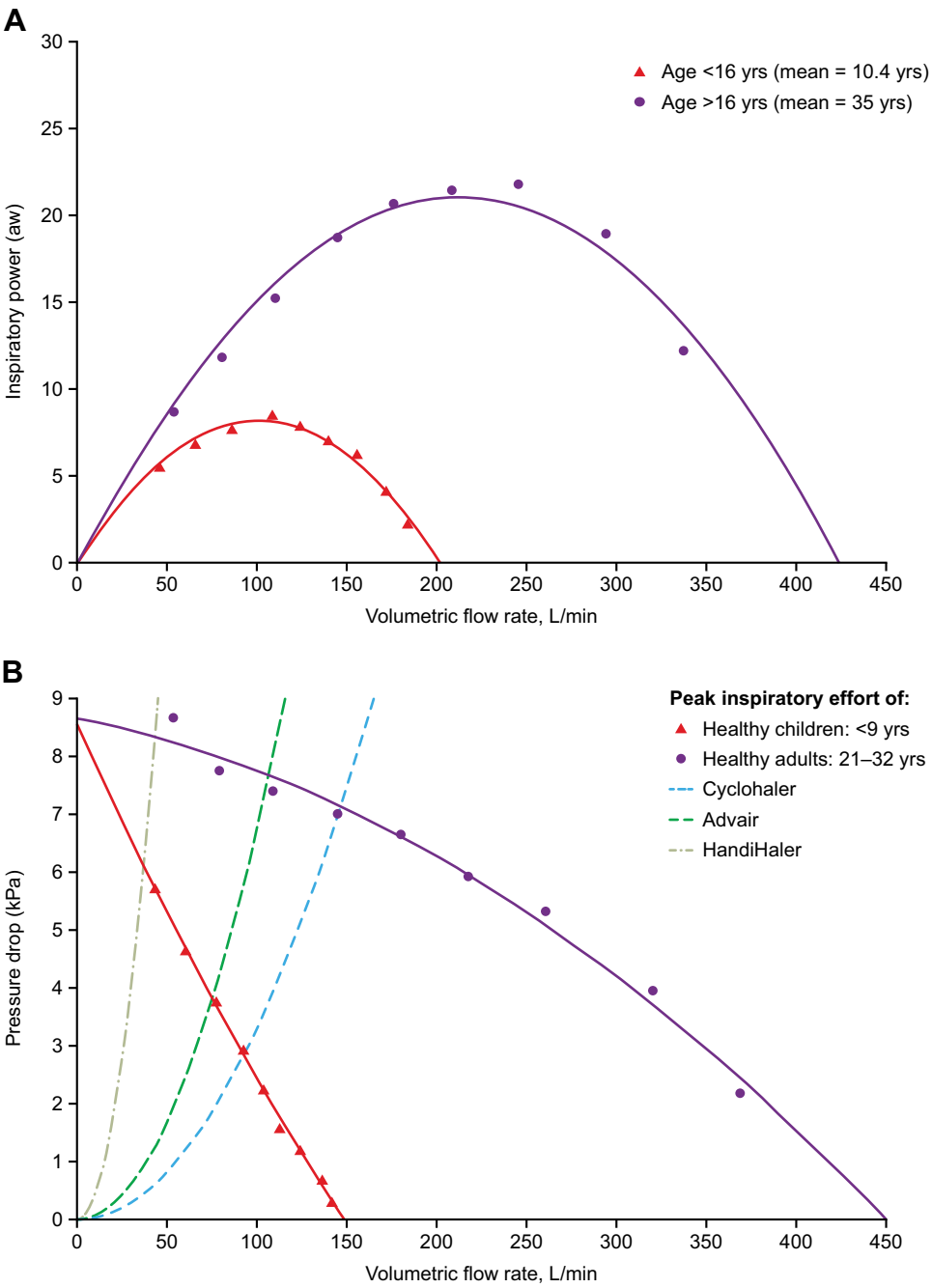


**Fig. 2** Inspiratory power curves for adults and children against volumetric flow rate (**A**) demonstrating the non-linear relationship between airflow and power, with maximum power achieved below maximum airflow. The power for deagglomeration of the active substance is generated by the patient's inspiratory manoeuvre. As power is the result of flow rate and differential pressure, inhalers must have some resistance for there to be power in the airflow through them. Estimated operating points of dry powder inhalers (DPIs) when used by healthy adults and children (**B**). Pressure-flow curves of three example DPIs and average operating points for adults and children are shown, illustrating that healthy adults can achieve higher pressure drops than healthy children. Cyclohaler® (Plastiape S.p.A., Osnago LC, Italy) is a low-resistance DPI, Advair® Diskus® (GSK, Brentford, UK) is a medium-resistance DPI and HandiHaler® (Boehringer Ingelheim, Ingelheim, Germany) is a high-resistance DPI. Reproduced with permission from Harris D. The Advantages of Designing High-Resistance Swirl Chambers for Use in Dry-Powder Inhalers. *ONdrugDelivery Magazine*, Issue 57 (Apr 2015):10–13.

is more important to consider initial inspiratory flow rather than peak inspiratory flow. In reality, evidence suggests that most patients can achieve the required inspiratory flow to use high resistance DPIs [1, 12].

For comparison, with pMDIs, overall inspiratory flow is more relevant to determine whether a patient is able to inhale the appropriate dose; therefore, the patient must inhale slowly and deeply using the correct technique [3]. Incorrect inhaler technique leads to suboptimal dosing and poor asthma control [4, 13].

## 2.5 How Valuable is the In-Check Dial in Making a Clinical Decision on a DPI?

The In-Check Dial is a commonly used tool that displays resistances of different pMDIs and DPIs [12, 14]. However, its use does have limitations in clinical practice. The relationship between devices is not linear and the clinical relevance of inhaler resistance is not clear [14]. Furthermore, the In-Check Dial only measures PIFR; it does not measure the acceleration rate or provide an indication that the full inspiratory manoeuvre was done correctly.

In clinical practice, the In-Check Dial can be a useful tool for HCPs to understand what the quick and deep inhalation required for a DPI versus the slow and steady inhalation required for a pMDI should look like. Without this aid, many people inhale far too quickly using pMDIs, thinking that they are inhaling slowly [12]. Patients also often use the device incorrectly or misinterpret the results.

Furthermore, according to the authors' experience, there is often a mismatch between a patient's inhalation manoeuvre using the In-Check Dial and their inhaler: a patient may breathe quickly using the In-Check Dial and slowly using their inhaler, or vice versa. This could be due to differences in the shape and size of the mouthpieces and different approaches to training versus the real-life use of an inhaler.

In summary, although the In-Check Dial can help with decisions, it is most relevant in determining whether a pMDI is suitable for a patient rather than to choose between DPIs.

### 2.6 What Difference Does Age or Disease Severity make on a Patient's Ability to Use a DPI, and Should this Factor into Prescribing Decisions?

The lungs are powered by muscles that are similarly strong in children older than 6 years, patients with COPD, and healthy adults, but these patient groups differ in their maximal inspiratory capacity on the basis of either lung size or disease severity [7, 8, 15]. However, even for high-resistance DPIs, an optimal flow rate of 40 L/min is achievable for most patients, irrespective of age or disease severity [7, 15, 16]. Therefore, patients are more likely to achieve a sufficient pressure drop with high-resistance rather than with low-resistance DPI devices [11]. However, age and frailty should still be considered in prescribing decisions, as these factors influence PIFR, dexterity and ability to use a particular device [3, 17]. Suboptimal PIFR or device use is associated with poorer health status [17].

### 2.7 What has Most Impact on Patient Outcomes—Device Choice or Inhaler Technique?

Inhaler technique and device choice are interlinked, but most guidelines recommend prescribing a device only after/in conjunction with teaching and assessing technique [18, 19]. Various factors influence inhaler choice (as previously discussed); however, provided a patient has the technical ability to use a given device, correct inhaler technique is the most important factor to achieving optimal patient outcomes. As different studies employ different device-specific checklists for assessing correct inhaler use, it can be difficult to directly compare studies on this topic [20]. However, the evidence generally suggests that clinical outcomes improve (e.g. reduced rates of disease exacerbation) when inhaler technique is correct [21, 22]. Research has also shown that appropriate PIFR was achieved by a significantly lower proportion of individuals with low-resistance devices than high-resistance devices, with inhaler technique (in particular, patients who failed to achieve PIFR inhaled too quickly) being a contributory factor [12]. This is also the case for different patient groups; most patients should be able to use their DPI effectively regardless of age or disease status [11]. In this respect, inhaler technique is key to ensuring selection of the right device for the right patient.

### 2.8 Why is it Important to Involve Patients in Device Selection?

The involvement of patients in their respiratory care is essential. Evidence suggests that involving patients in the selection of their inhaler device may promote their adherence to treatment [3]. Studies have shown that switching inhaler types without consulting with the patient results in worse disease control and treatment outcomes [23]. Conversely, patient involvement in inhaler choice and satisfaction with the device have been shown to lead to better outcomes, including improved quality of life, fewer healthcare challenges, and fewer exacerbations [24]. Involving patients in decisions regarding their care all along the patient pathway has now been set as a national healthcare vision in the UK on the basis of the concept of shared decision-making [25].

## 3 Conclusion

While most people would achieve better clinical outcomes with a high-resistance DPI than with a low-resistance DPI, inhaler resistance alone should not be used to make prescribing decisions. Correct inhaler technique (including inspiratory flow), treatment adherence and patient preference have a greater impact on disease outcomes than the indiscriminate choice of any specific device. The key objective is to make sure the right device is selected for the right patient.

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## Declarations

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**Ethics Approval** Not applicable

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