Is a Pressure Drop ≥10 cm H_2O with any Dry Powder Inhaler (DPI) a Reasonable Threshold Above which a Patient Should Receive an Adequate Lung Dose: Method Validation and Experience with a Sample Cohort of COPD Patients?

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Summary

It has been claimed that an adequate lung dose should be received above a threshold pressure drop of 10 cm H_2O with any DPI, based on the negative pressure generated by the patient's inspiratory effort. We report first the validation of a volumetric flow sensor/recorder simulating adult inhalation in accordance with a standard sinus flow rate-time waveform. We then used this sensor as validated to record flow profiles from 5 patients with varying severity of COPD familiar with the Turbuhaler* DPI, inhaling from a placebo Turbuhaler*, representing a DPI having medium flow resistance. Maximum inspiratory pressures were 19.2, 11.5, 12.7, 33.3 and 50.0 cm H_2O for patients A to E. In the laboratory, we recreated each inhalation profile via the breathing simulator-anatomical model oropharynx coupled to the mouthpiece of a Symbicort* Turbuhaler* DPI. The simulator was located distal to a microbial collection filter, positioned at the exit of a model adult oropharynx, to capture medication likely to have deposited at the carina and therefore potentially available for lung delivery. The corresponding mass of budesonide and formoterol components (n = 3 replicates, mean ± SD) recovered from the model mimicking these inspiratory flow rate-time profiles varied widely from 13.6 ± 3.3 to 35.3 ± 1.4 µg budesonide and from 0.7 ± 0.1, to 1.8 ± 0.1 µg formoterol. These findings highlight the value in discussion around what is an 'adequate' lung dose and what other factors, in addition to pressure drop, may be involved.

Key Message

This laboratory simulation re-created previously generated inhalation profiles from COPD patients to assess medication delivery from the same medium resistance DPI via a model oropharynx to a collection filter with highly variable outcomes that were related to inhalation duration and maximal inspiratory pressure.

Introduction

DPIs have a wide range of inhalation flow resistance [1], and it is therefore important to understand how the patient inhalation profile might influence the efficiency of medication delivery [2]. To this end, Clark *et al.* have claimed, based on the negative pressure generated by the patient's inspiratory effort, a pressure drop ~≥10 cm H_2O with any DPI is a threshold above which an adequate lung dose should be received [3]. The present study was undertaken in two parts with the following purposes: (a) to validate a model aerosol collection filter-adult oropharyngeal model-breathing simulator system against a standardized inhalation flow profile generated by the in-house breathing simulator; (b) to use that system to assess DPI-delivered medication delivery from inhalation profiles captured from a small cohort of COPD patients selected at random. The goal was to ascertain if the inhalation profile, in particular the maximal inspiratory pressure (MIP), influenced medication delivery efficiency by collecting the aerosol on the filter, representing the portion of the inhaled dose capable of reaching the carina and therefore potentially available for delivery to the lungs.

Experimental Methods

In the first part of the study, we validated the response from a passive flow differential pressure converter based pneumotachometer sensor (SpiroQuant H, Honeywell-Envitec, Wismar, Germany) capable of simultaneously measuring the volumetric flow-elapsed time profile and peak inspiratory

pressure, in conjunction with a breath recorder (Hans Rudolph SmartLab* series 1140, Shawnee, KS, USA) sampling at 200 Hz, by coupling it to our previously calibrated in-house breathing simulator (ASL5000, Ingmar Medical, Pittsburgh, PA). The breath simulator was set to recreate the Canadian Standard adult breathing profile having a nominal tidal volume of 500 ml, inspiratory/expiratory (I:E) ratio of 0.50, with a rate of 12 breaths/min [4]. The sensor was oriented in the flow path as described by its manufacturer.

In the second part of the investigation, a small cohort of volunteer male patients (n = 5, designated A to E) with varying COPD severity (aged 57-83), and who were familiar with the Turbuhaler* DPI, were recruited to inhale from a placebo version of the medium flow resistance Turbuhaler* DPI (AstraZeneca Mölndal, Sweden (Figure 1A)). Each inhalation profile was recorded using the purpose-constructed attachment to the pneumotachometer evaluated in the first part of the study. In the laboratory, each inhalation flow profile was subsequently replayed via the breathing simulator (n = 5 replicates). In this configuration, the mouthpiece of a Symbicort* Turbuhaler* DPI containing active formulation (100 µg budesonide (BUD) + 6 µg formoterol fumarate (FF) per actuation)) was attached to a model adult oropharynx [5]. A bacterial/viral filter was located at the distal end of the model and then to the breathing simulator (Figure 1B) to capture the portion of the dose penetrating to the carina and therefore potentially capable of lung delivery. The mass of each API recovered from the filter was subsequently assayed by an HPLC-spectrophotometric method.

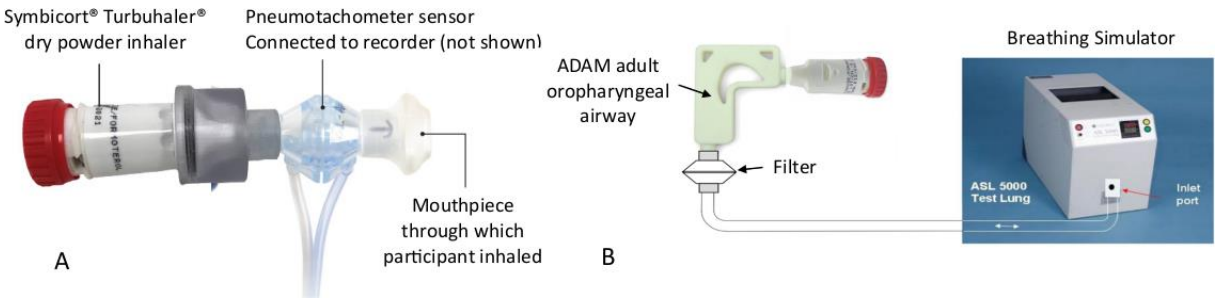


Figure 1: (A): Set-up for Acquiring Patient Inhalation Waveforms; (B) Arrangement for Assessing Medication Delivery via the Adult Oropharynx Model to a Bacterial/Viral Filter Located to Mimic Particle Penetration to the Carina

Results

The pneumotachometer validation data are summarized in Table 1:

Table 1: Inhalation Flow Waveform Characteristics from SpiroQuant* H flow sensor with Hans Rudolph Breath Recorder Responding to the Canadian Standard Normal Adult Profile compared with Metrics Reported by the ASL5000 Breathing Simulator

Metric	Canadian Standard Reference Profile	Mean Values Reported by Spiroquant* Q Flow Sensor/Hans Rudolph Recorder	Mean Values Reported by ASL 5000 Breath Simulator
Tidal Volume (ml)	**500**	**500.5**	**506.4**
I:E ratio	**0.50**	**0.56**	**0.53**
Breathing Cycles/min	**12**	**13.0**	**12.9**

The tidal volume reported by the flow sensor/recorder was almost identical with the standard value, with the value provided by the breathing simulator being only 1.2% higher. The I:E ratios determined

by either method were slightly greater than the nominal value of 0.50, and the breathing rates were correspondingly longer. However, the divergence between the measures from the two techniques were only 5.6% and 1.0% for I:E ratio and breathing rate respectively. The flow sensor/recorder was therefore deemed suitable for obtaining the patient-generated inhalation profiles.

The COPD patient-generated flow rate-time profiles together with the corresponding maximum inspiratory pressure (MIP) values, are shown in Figure 2.

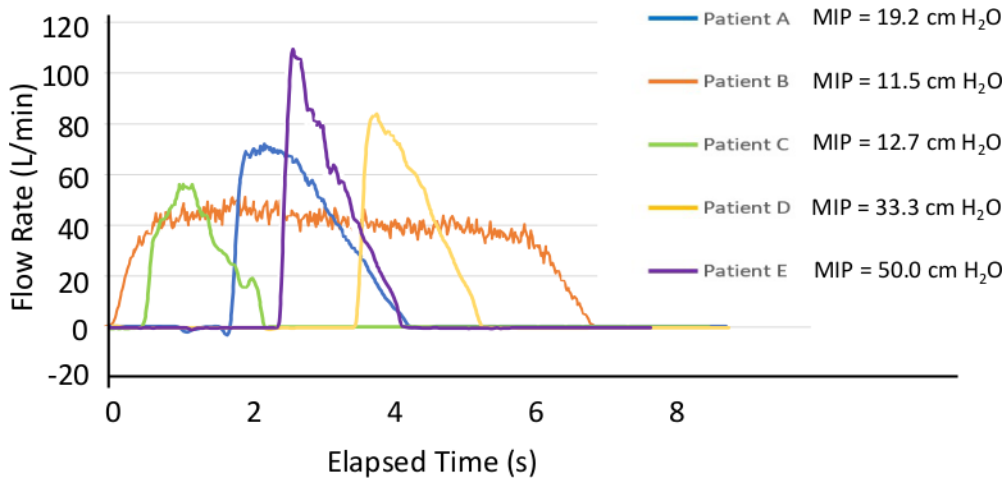


Figure 2: Flow Rate-Elapsed Time Profiles Recorded from the Signal Generated by a Validated Spiroquant H sensor by Patients Having Differing Degrees of COPD Inhaling from a Placebo TurbuHaler*

The variation in start times for the various inhalation profiles is shown explicitly rather than normalizing the data to begin at 0 s elapsed time to show the differing amount of delay from patient to patient.

The inhalation flow rate-time profiles varied greatly from one patient to another in terms of both amplitude and duration, with an associated variability in MIP values ranging from a minimum value of 11.5 cm H_2O (patient B) to a maximum of 50.0 cm H_2O (patient E). Peak inspiratory flow rates exceeded 30 L/min for all patients, a threshold reported by Broeders *et al*. [6] as being sufficient for the Turbuhaler* DPI to provide a therapeutic dose, although these authors also observed that a flow rate > 60 L/min would be required for optimum medication delivery to the lungs.

The mass of budesonide and formoterol components of Symbicort* collected on the filter distal to the model oropharyngeal airway (mean ± S.D.) are presented in Figure 3. The upper airway deposition (within the model airway) was recorded, with similar variability to the mass of each API recovered from the filter.

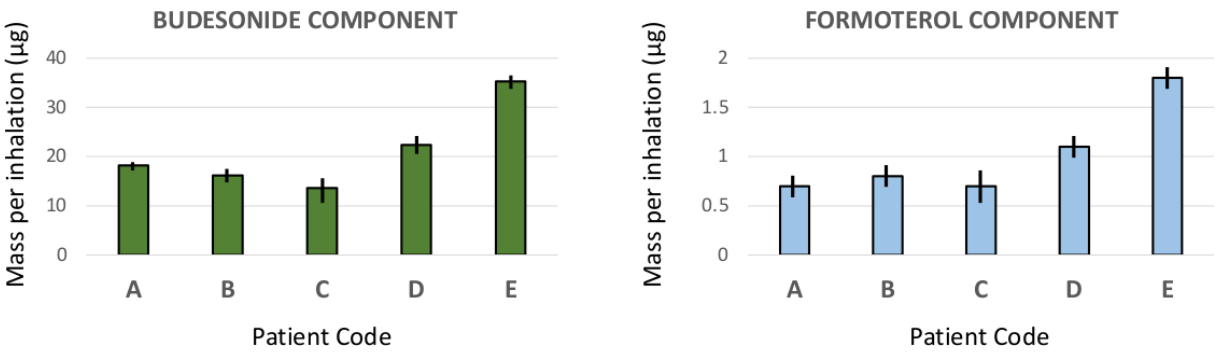


Figure 3. Mass of Each Component from a Symbicort* Turbuhaler* DPI Deposited on Filter Distal to the Adult Model Oropharyngeal Airway Obtained using a Breathing Simulator to recreate the COPD Patient A to E Breathing Patterns Recorded by the Pneumotachometer

The replicate measures per patient-generated inhalation profile for each component were generally consistent, with coefficients of variation <10%, except for the data from patient C where the two coefficients of variation close to 25% without an assignable cause. More importantly, the mass of either component varied widely from one inhalation profile to another, with the largest values (35.3 ± 1.4 µg budesonide; 1.8 ± 0.1 µg formoterol) associated with patient E, who generated the highest MIP (50.0 cm H_2O) and inhaled for the shortest duration (1.8 s). Conversely, the next to smallest masses of each component (16.2 ± 1.5 µg budesonide; 0.8 ± 0.1 µg formoterol) were recovered when the inhalation profile generated by patient B, who had the lowest MIP (11.5 cm H_2O), inhaling for the longest duration (6.8 s).

Discussion

The large variability in the inhalation profiles was expected, as it has previously been observed in at least one carefully designed observational study that such variability exists with COPD patients when instructed to inhale through their usual device without training to achieve a target maneuver [7]. An obvious limitation of the present investigation is the small patient cohort size. Plans were made to increase the number of volunteer patients in the cohort, before the COVID-19 pandemic restrictions curtained such activity. A further limitation is that only a single profile was obtained per patient rather than the best of several attempts. In defence of this approach, the intention was not to train the patients, but to observe how they were normally using the inhaler. Once these restrictions have been lifted, further efforts will be made to expand patient numbers as well as to extend the investigation to examine how the trends observed presently apply with lower and higher resistance DPIs. However, the present findings as they stand, indicate that setting a MIP threshold of just 10 cm H_2O to receive an adequate lung dose, as proposed by Clark *et al*. [1] may be an insufficient criterion. There is therefore likely to be potential value in having further discussion about these questions:

a) what is an adequate dose?
b) what other factors, in addition to MIP, may be important in achieving that target?

Conclusions

This *in vivo-in vitro* investigation with a medium resistance DPI indicated large differences in breathing profiles and consequently large differences in observed drug delivery. It has therefore highlighted a potential mismatch between a proposed lower limit of 10 cm H_2O for MIP and likely medication delivery efficacy to the lungs of

patients with COPD. Notwithstanding the limitation of a small cohort of patient profiles, we believe there is merit in further discussions around what is an ‘adequate’ lung dose and what other factors, in addition to pressure drop, may be involved.

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