Original Research Article

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Inspiratory flow patterns with dry powder inhalers of low and medium flow resistance in patients with pulmonary arterial hypertension

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Abstract

Inhalation profiles to support use of dry powder inhalers for drug delivery in patients with pulmonary arterial hypertension have not been reported. We aimed to evaluate the inspiratory flow pattern associated with low and medium flow resistance dry powder inhaler devices (RS01-L and RS01-M, respectively) in patients with pulmonary arterial hypertension. This single-center study enrolled patients with pulmonary arterial hypertension associated with connective tissue disease ($n = 10$) and idiopathic pulmonary arterial hypertension ($n = 10$) to measure the following inhalation parameters: inspiratory effort (kPa), peak inspiratory flow rate (L/min), inhaled volume (L), and flow increase rate (L/s^2) using the two devices. We identified a trend toward higher mean pulmonary artery pressure in the idiopathic pulmonary arterial hypertension group (50 ± 13 mmHg vs. 40 ± 11 mmHg in pulmonary arterial hypertension associated with connective tissue disease; $p = 0.077$). On average, peak inspiratory flow rate was higher with RS01-L vs. RS01-M (84 ± 19.7 L/min vs. 70.4 ± 13.2 L/min; $p = 0.015$). In the overall group, no differences between RS01-L and RS01-M were observed for inhaled volume, inspiratory effort, or flow increase rate. Inhaled volume with RS01-L was higher in pulmonary arterial hypertension associated with connective tissue disease vs. idiopathic pulmonary arterial hypertension patients: 1.6 ± 0.4 L vs. 1.3 ± 0.2 L; $p = 0.042$. For the RS01-L, inhaled volume correlated with forced expiratory volume in one second ($r = 0.460$, $p = 0.030$) and forced vital capacity ($r = 0.507$, $p = 0.015$). In patients with pulmonary arterial hypertension associated with connective tissue disease using RS01-L, both inspiratory effort and flow increase rate were highly correlated with pulmonary vascular compliance ($r = 0.903$, $p = 0.0001$ and $r = 0.906$, $p = 0.0001$; respectively); while with RS01-M, inspiratory effort was highly correlated with pulmonary vascular compliance ($r = 0.8$, $p = 0.001$). Our data suggest that the use of RS01-L and RS01-M dry powder inhaler devices allowed adequate inspiratory flow in pulmonary arterial hypertension patients. The correlation between flow increase rate and pulmonary vascular compliance in pulmonary arterial hypertension associated with connective tissue disease deserves further investigation.

Keywords

pulmonary arterial hypertension (PAH), dry powder inhaler (DPI), inhalation profile, drug delivery

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Introduction

Dry powder inhalers (DPIs) are increasingly used to provide drug delivery directly to the lungs. Compared with other routes of drug delivery, preparations that are specifically designed for inhalation can offer benefits in pulmonary arterial hypertension (PAH) with direct delivery to the site of disease. Inhalational approaches can result in higher pulmonary drug concentrations with lower systemic side effects and more rapid onset of action without first-pass metabolism.[1]

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Efficient drug distribution is dependent on performance characteristics of a DPI.[2] Specifically, inspiratory flow generated by the subject and the resultant turbulence generated inside the device are features that determine, in part, the aerosol performance of the formulation and consequent distribution of drug throughout the airways.[1,2] An adequate interaction between these two factors is obligatory for optimal device performance in the context of the specific drug formulation.

Previous studies have focused on the importance of peak inspiratory flow (PIF), demonstrating that optimal drug delivery was achieved if the PIF was at least 60 L/min for rapid-acting β2-agonists delivered via DPI with a particular formulation (i.e. micronized blend) in the treatment of moderate–severe acute asthma and chronic obstructive pulmonary disease (COPD) in the elderly.[2,3] However, flow rates < 60 L/min can be achieved with low-density engineered particles via spray drying.[4,5] Inspiratory flow is dependent upon PIF, flow increase rate (FIR), and inhaled volume (Inh V).[6] Alterations in the individual components of PIF also can affect overall drug delivery.[2,6] Moreover, the quality of the inspiratory flow may be influenced by patient's effort and technique, functional anatomy and physiology of the upper and lower airways, and the functional properties of the lungs including mucosa, connective tissue, and neural and lymphatic tissues.[7] A number of common conditions can significantly impact flow patterns in the airways, including obesity, pregnancy, airway disease, and parenchymal lung diseases. New evidence supports the importance of FIR, suggesting that the initial ramp during the inspiratory maneuver could also have a crucial role in the total dose delivered to the lungs.[8]

DPIs are categorized according to their intrinsic resistance to airflow as low, medium, and high resistance devices.[9] The combination of device resistance along with its dispersion mechanism, aerosol properties of the drug formulation, and the negative pressure generated by patient inspiratory effort (Insp Eff) determines whether optimal drug delivery is achieved. Since patients tend to generate similar pressure drops across different devices, the inspiratory flow rate required to achieve a similar level of drug delivery is typically inversely related to device resistance, assuming similar drug formulation and device design.[9,10]

In patients with COPD, age and sex have been found to be independent predictors of PIF, with no clear correlation with forced expiratory volume in one second (FEV_1).[11] Other studies have evaluated the performance of DPIs in asthma[12] and cystic fibrosis.[9] In patients with advanced PAH, significant end expiratory airflow limitation, premature airway closure, and reduced vital capacity may be observed.[13] However, little is known about the impact of PAH on the inspiratory flow pattern. The present study was designed to generate and evaluate data from patients with PAH in order to model dry powder inhalation and distribution into the airways to aid in selecting an appropriate flow resistance for the RS01 DPI device.

Methods

Study population and study design

In this single-center observational study, 20 PAH patients recruited from the pulmonary vascular disease clinic at Brigham and Women's Hospital (Boston, MA) were enrolled between April and August of 2019. PAH was diagnosed by a clinically indicated resting supine right heart catheterization (RHC). Patients were included based on the following criteria: (1) PAH was defined by mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and pulmonary vascular resistance > 3 WU,[14] and (2) documented lung function data assessed by spirometry within a year prior or up to one month after enrollment. Exclusion criteria included: (1) PAH other than idiopathic or heritable PAH (iPAH) or connective tissue disease associated PAH (aPAH), (2) left heart disease defined by more than mild mitral and/or aortic valvular disease or left ventricular ejection fraction < 0.50 on resting echocardiography, or postcapillary pulmonary hypertension defined by a mPAP ≥ 25 mmHg and PAWP > 15 mmHg at resting RHC, (3) relevant lung disease defined by FEV_1 divided by forced vital capacity (FVC) < 0.7 associated with $FEV_1 < 60\%$ predicted, or a radiological diagnosis of lung fibrosis[15]; and/or (4) inability to comply with the protocol-required procedures. The study protocol was approved by Partners Healthcare Human Research Committee (2018P002389). Patients provided written informed consent.

Inspiratory flow assessment

Each subject was asked to perform five inspiratory maneuvers with each device, using either a RS01 low-resistance (RS01-L) (Plastiape; Osnago, Italy) or a RS01 medium-resistance (RS01-M) DPI first. After 10 min of rest, five additional inspiratory maneuvers were performed using the alternate device (RS01-L or RS01-M). A 30-s pause was required between each Insp Eff. The decision regarding initial DPI was based on a crossover design, so that the devices were alternated every five patients, starting with RS01-L.

The inspiratory profile for each patient was recorded while inhaling through a low-resistance (RS01-L (0.06R)) and a medium resistance (RS01-M (0.08R)) DPI device (Plastiape S.p.A, 23875 Osnago-Lecco, Italy; Fig. 1), with an empty size 3 capsule (Capsugel Mfg Inc, G3ICS001056) loaded into the piercing chamber (Fig. 1). The DPI was inserted into a device adapter which was then attached to a disposable mouthpiece (Qosina, p/n 56013 or equivalent) and Respirgard filter (Airlife Model 303EU or equivalent) assembly. A pressure tap located on the device adapter was

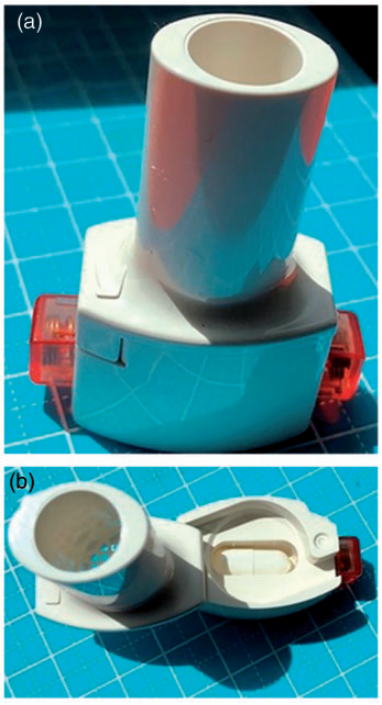

Fig. 1. Plastiape RS01 dry powder inhaler; (a) mouthpiece closed position and (b) mouthpiece open with capsule loaded into piercing chamber.

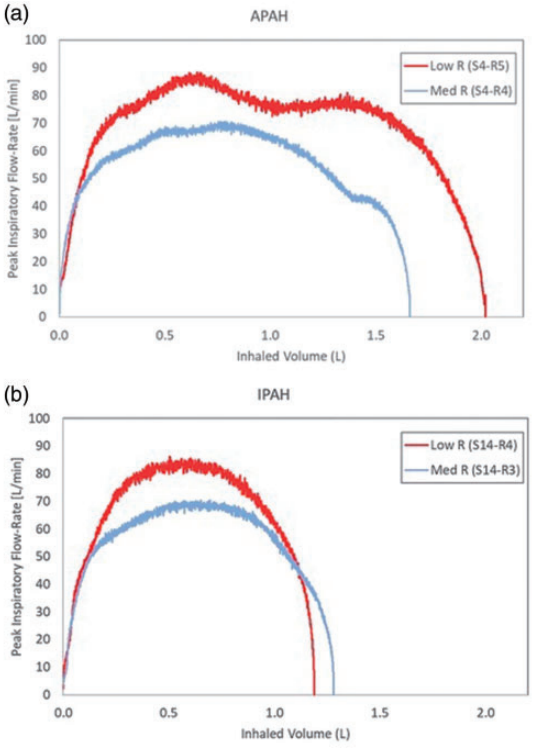

Fig. 2. Example inspiratory flow profiles for low and medium RS01 flow resistance inhalers; (a) aPAH and (b) iPAH, where "R" represents flow resistance.

then connected to an inhalation pressure recorder box (iPharma Ltd, San Francisco, CA), containing a pressure transducer and data acquisition system. Recorded patient inhalation pressure profiles were then used to determine the following inspiratory parameters: Insp Eff (kPa), PIF (L/min), Inh V (L), and FIR (L/s^2) (Fig. 2).

The relationship between inhaler pressure drop and volumetric flow was determined from the following equation

$$R = \frac{\sqrt{DP}}{Q}$$

where R is the inhaler flow resistance ($cm \times H_2O^{0.5}/L/min$), DP is the inhaler pressure drop (centimeter of water), and Q is the peak inspiratory volumetric flowrate (L/min).[16]

R for each inhaler (i.e. 0.06 and 0.08 R for RS01-L and RS01-M, respectively) was known, while DP was obtained through inspiratory profile measurements.

Statistical analysis

Data for continuous variables are presented as mean ± standard deviation. Data for categorical variables are presented as absolute numbers and/or percentages. Group comparisons were performed using a paired t test. One-way ANOVA with Tukey's post hoc analysis was used when comparing aPAH/RS01-L, iPAH/RS01-L, aPAH/RS01-M, and iPAH/RS01-M subgroups. A Pearson correlation coefficient was calculated to determine whether patient and clinical characteristics correlated with inspiratory flow pattern. $P < 0.05$ was considered statistically significant. All statistical analysis was performed with GraphPad Prism 7 (GraphPad Software).

Results

Baseline characteristics

Twenty patients (19 females), mean (standard deviation) age of 63 ± 14.91 years, 10 with iPAH and 10 with aPAH (9 associated with systemic sclerosis and 1 with mixed connective tissue disease) were enrolled and completed the study (Table 1). No differences in age, body mass index, oxygen saturation measured by pulse oximetry, and/or lung function assessed by spirometry was observed between groups. Six patients (60%) with aPAH and three (30%) with iPAH were World Health Organization (WHO) functional class 3. There was a trend toward higher mPAP in the iPAH group (50 ± 13 mmHg vs. 40 ± 11 mmHg in aPAH; $p = 0.077$). A higher total pulmonary resistance (12.8 ± 4.8 WU vs. 8.4 ± 3.3 WU; $p = 0.030$) was observed in the iPAH population. Chest CT imaging was available in 8 of 10 aPAH and 7 of 10 iPAH patients. Based on investigator assessment, all patients had no more than mild interstitial lung disease. Mild interstitial lung changes were observed in six (75%) aPAH and one (14%) iPAH patients.

Table 1. Baseline demographics and disease characteristics ($n = 20$).

	aPAH ($n = 10$)	iPAH ($n = 10$)	p Values
Characteristic			
Age, years	63 ± 12	62 ± 18	0.896
Male/female, n	1/9	0/10	0.330
Body mass index, kg/m^2	28.2 ± 8.1	27.5 ± 8.8	0.863
WHO FC I/II/III/IV, n	2/2/6/0	3/4/3/0	0.295
SpO_2 at rest, %	94 ± 4	92 ± 6	0.339
Pulmonary function test			
FEV_1, L	1.7 ± 0.4	1.7 ± 0.6	0.862
FEV_1, % predicted	74.0 ± 15.0	70.0 ± 11.0	0.502
FVC, L	2.0 ± 0.5	2.0 ± 0.7	0.984
FVC, % predicted	67.0 ± 12.0	66.0 ± 13.0	0.903
FEV_1/FVC	85.0 ± 4.0	83.0 ± 6	0.385
Right heart catheterization			
Heart rate, beats/min	77.0 ± 10.0	76.0 ± 11.0	0.867
RAP, mmHg	8.0 ± 4.0	9.0 ± 5.0	0.903
mPAP, mmHg	40.0 ± 11.0	50.0 ± 13	0.077
PAWP, mmHg	10.0 ± 3.0	10.0 ± 4.0	0.600
TPG, mmHg	31.0 ± 11.0	40.0 ± 14.0	0.119
CO, L/min	5.0 ± 1.1	4.2 ± 1.5	0.231
CI, L/min/m^2	2.7 ± 0.5	2.4 ± 0.5	0.186
TPR, WU	8.4 ± 3.3	12.8 ± 4.8	0.030
PVR, WU	6.4 ± 3.3	9.4 ± 4.8	0.118
PVC, mL/mm Hg	1.9 ± 1.0	1.2 ± 0.3	0.112

Notes: Continuous variables are presented as mean ± SD; categorical data as n or n (%).
aPAH: associated pulmonary arterial hypertension; CI: cardiac index; CO: cardiac output; FC: functional class; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; iPAH: idiopathic pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVC: pulmonary vascular compliance; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SpO_2: arterial oxygen saturation measured by pulse oximetry; TPG: transpulmonary gradient; TPR: total pulmonary resistance; WHO: World Health Organization; WU: Wood units.

Table 2. Inspiratory flow pattern in PAH according to device resistance ($n = 20$).

Variables	RS01-L	RS01-M	p Values
FIR 20–30, L/s^2	5.7 ± 3.8	4.5 ± 2.1	0.235
PIF, L/min	84.0 ± 19.7	70.4 ± 13.2	0.015
Inspiratory effort, kPa	2.6 ± 1.2	3.2 ± 1.1	0.121
Inhaled volume, L	1.4 ± 0.3	1.3 ± 0.3	0.267

Note: Data are presented as mean ± SD.
FIR: flow increase rate; PIF: peak inspiratory flow rate; RS01-L: low resistance device; RS01-M: medium resistance device.

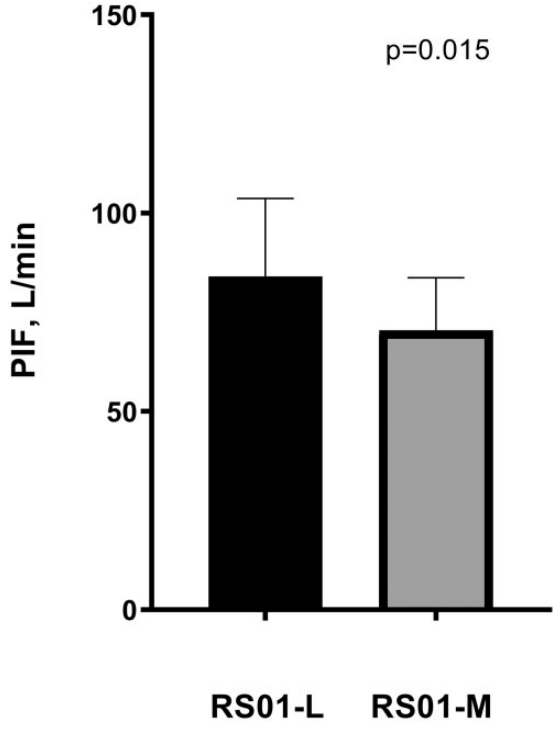

Fig. 3. Peak inspiratory flow in RS01-L vs. RS01-M ($n = 20$).
PIF: peak inspiratory flow; RS01-L: low resistance device; RS01-M: medium resistance device.

Inspiratory flow pattern

Overall, regardless of disease subgroup, PAH patients achieved a higher PIF with RS01-L when compared to RS01-M. No differences were observed in Inh V, Insp Eff, or FIR (Table 2 and Fig. 3). When the inspiratory profile was analyzed according to PAH group, only RS01-L Inh V differed between groups (1.6 ± 0.4 L in aPAH vs. 1.3 ± 0.2 L in iPAH; $p = 0.042$) (Supplementary material, Tables S1 and S2 and Fig. 4).

There were statistically significant differences in PIF and Inh Vol between aPAH/RS01-L and iPAH/RS01-M as determined by one-way ANOVA ($p = 0.016$ and 0.031, respectively) (Table 3).

Correlation of inspiratory flow pattern with clinical parameters and right heart hemodynamics

In the overall population using RS01-L, age inversely correlated with PIF ($r = –0.463$, $p = 0.035$) and Insp Eff ($r = –0.474$, $p = 0.025$). In contrast, no such correlation was observed with RS01-M. With regard to lung function, when patients used both, the RS01-L and RS01-M inhalers, the spirometric variables showed different correlations with the inspiratory profile. Using the low resistance device (RS01-L), all patients ($n = 20$) regardless of PAH subgroup, displayed correlation of FIR with systolic pulmonary arterial pressure (sPAP) ($r = –0.465$, $p = 0.038$), mPAP ($r = –0.475$, $p = 0.034$), transpulmonary gradient (TPG) ($r = –0.503$, $p = 0.023$), and pulmonary vascular compliance (PVC) ($r = 0.659$, $p = 0.001$). Although a similar trend was observed with RS01-M, only a positive correlation of Insp Eff with PVC ($r = 0.516$; $p = 0.019$) was observed. Correlation between clinical parameters, respiratory supine hemodynamics, and inspiratory flow pattern in the

overall population is included in the supplementary material.

When PAH subgroups were analyzed separately, we observed that FIR and Insp Eff correlated with hemodynamics in aPAH patients, using both the RS01-L and RS01-M devices (Tables 4 and 5 and Fig. 5), while in iPAH patients, correlation with hemodynamics was observed only with PIF (Supplementary Material, Tables S4 and S5). In patients with aPAH, Insp Eff was highly correlated with PVC ($r = 0.903$, $p = 0.0001$) and FIR with PVC ($r = 0.906$, $p = 0.0001$) with the RS01-L device. When evaluating the RS01-M device, Insp Eff was highly correlated with PVC ($r = 0.81$, $p = 0.001$) (Tables 4 and 5 and Fig. 5).

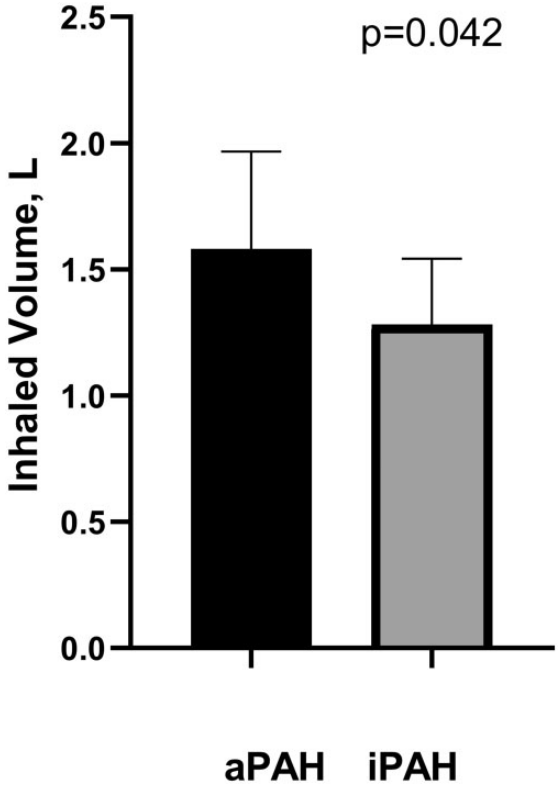

Fig. 4. RS01-L inhaled volume in aPAH vs. iPAH ($n = 20$).
aPAH: associated pulmonary arterial hypertension; iPAH: idiopathic pulmonary arterial hypertension.

Discussion

The main findings of this observational study evaluating DPI-related inspiratory flow pattern in PAH patients are: (1) patients with PAH are able to generate the inspiratory flow required to use the RS01-L and RS01-M devices and (2) right heart hemodynamics showed a correlation with FIR and Insp Eff in aPAH, but only with PIF in iPAH. FIR in aPAH was impacted by the degree of pulmonary vascular remodeling as measured by PVC.

Taken together, these observations may be useful in selecting the appropriate air flow resistance for a device in patients with PAH. This is the first study, to the best of our knowledge, to describe the inspiratory flow pattern in PAH. DPI performance is influenced by several factors including the inspiratory flow (dependent on patient's inspiratory maneuver and airways and lung conditions), the device's intrinsic resistance to the airflow, and the drug formulation.[1,2] Additionally, other factors related to the patient, such as instructions provided, clinical parameters, age, gender, training, and smoking history likely influence the character of airflow throughout the Insp Eff.[7,17]

In a concept review of DPIs, Dal Negro indicated that the effective delivery of drug powder was dependent on the inspiratory flow rate of the patient and the intrinsic resistance of the device, and argued that the interaction of these two factors could result in improved performance for a medium resistance device compared to a low resistance device.[17] However, this interaction is dependent on the drug formulation and the aerosol properties of that formulation in a particular device. The formulation itself will likely determine the optimal resistance of the device that should be used, and the choice of a particular DPI for a particular drug formulation needs to be determined in testing of the drug–device combination. There is great interest in the development of formulations that maintain the desirable aerosol properties across a range of inspiratory flow rates. For example, aclidium bromide (Genuair) showed flow-rate independence across a range of flow rates.[18] Our study provides data regarding the range of inspiratory flow rates observed in a cohort of PAH patients and could therefore be useful in understanding the range of flow rates for

Table 3. Comparison of inspiratory flow pattern according to device resistance and disease subgroup ($n = 20$).

	aPAH ($n = 10$)		iPAH ($n = 10$)		
Variable	RS01-L	RS01-M	RS01-L	RS01-M	ANOVA p Values
FIR 20–30, L/s^2	6.2 ± 4.5	4.5 ± 1.9	5.1 ± 3.2	4.4 ± 2.5	0.597
PIF, L/min	90.9 ± 20.0	74.2 ± 15.0	77.0 ± 17.7	66.6 ± 10.5[a]	0.016
Inspiratory Effort, kPa	2.4 ± 1.2	3.0 ± 1.3	2.8 ± 1.1	3.4 ± 1.0	0.326
Inhaled Volume, L	1.6 ± 0.4	1.4 ± 0.3	1.3 ± 0.2	1.2 ± 0.2[a]	0.031

[a]$p < 0.05$ when compared with aPAH/RS01-L.
Note: Data are presented as mean $\pm$ SD.
aPAH: associated pulmonary arterial hypertension; FIR: flow increase rate; iPAH: idiopathic pulmonary arterial hypertension; PIF: peak inspiratory flow rate; RS01-L: low resistance device; RS01-M: medium resistance device.

Table 4. Correlations between clinical parameters and resting supine hemodynamics with inspiratory flow pattern with RS01-L in patients with aPAH ($n = 10$).

Variables	Peak inspiratory flow rate, L/min		Inhaled volume, L		Inspiratory effort, KPa		Flow increase rate 20–30, L/s^2	
	r	*p* Values	*r*	*p* Values	*r*	*p* Values	*r*	*p* Values
Age, years	–0.441	0.151	–0.479	0.114	–0.458	0.133	0.334	0.287
WHO functional class	0.348	0.266	–0.207	0.518	0.338	0.281	0.183	0.568
Pulmonary function test								
FEV_1, % predicted	0.435	0.157	0.303	0.337	0.415	0.178	0.645	0.023
FVC, % predicted	0.274	0.387	0.521	0.081	0.245	0.442	0.360	0.249
FEV_1/FVC	0.839	0.0006	–0.146	0.649	0.863	0.0003	0.646	0.023
Right heart catheterization								
RAP, mmHg	–0.072	0.824	–0.665	0.018	–0.678	0.015	–0.315	0.317
sPAP, mmHg	0.294	0.353	–0.094	0.771	–0.782	0.002	–0.665	0.018
dPAP, mmHg	0.281	0.375	–0.019	0.951	–0.724	0.007	–0.600	0.039
mPAP, mmHg	0.260	0.413	0.001	0.996	–0.738	0.006	–0.644	0.023
PAWP, mmHg	0.636	0.026	–0.349	0.266	0.042	0.895	0.032	0.919
TPG, mmHg	0.092	0.774	0.088	0.783	–0.724	0.007	–0.630	0.027
PP, mmHg	0.294	0.352	–0.162	0.614	–0.756	0.004	–0.538	0.070
SV, mL	–0.022	0.944	–0.477	0.116	0.487	0.108	0.700	0.011
CO, L/min	–0.033	0.918	–0.188	0.557	0.361	0.247	0.568	0.053
CI, L/min/m^2	–0.094	0.771	–0.195	0.542	0.662	0.018	0.821	0.001
HR, beats/min	0.004	0.989	0.652	0.021	0.044	0.890	0.018	0.953
TPR, WU	0.210	0.512	0.104	0.746	–0.672	0.016	–0.686	0.013
PVR, WU	0.0281	0.930	0.168	0.601	–0.601	0.038	–0.617	0.032
PVC, mL/mm Hg	–0.179	0.576	–0.018	0.954	0.903	0.0001	0.906	0.0001

Note: $p < 0.05$ = statistically significant.

r: Pearson correlation; CI: cardiac index; CO: cardiac output; dPAP: diastolic pulmonary artery pressure; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HR: heart rate; PAWP: pulmonary arterial wedge pressure; PP: pulse pressure; PVC: pulmonary vascular compliance; PVR: pulmonary vascular resistance; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; SV: stroke volume; TPG: transpulmonary gradient; TPR: total pulmonary resistance; WHO: World Health Organization; mPAP: mean pulmonary arterial pressure.

which drug performance should be maintained in this patient population.

Inspiratory profile in PAH

Our observations support the use of both low and medium resistance devices in PAH, as most patients were able to generate minimum PIF values (or inspiratory eff) > 50 L/min (>1 kPa) that is considered to be sufficient for low and medium resistance devices when pairing with engineered particle formulation.[4,10,11] Although previous studies have been performed with different devices and/or air flow resistance characteristics, in concordance with our study, others have observed optimal PIF when DPIs were tested in COPD,[11] asthma,[12] and cystic fibrosis.[9]

When evaluating dose delivery by DPIs, previous investigations have focused on PIF,[19–21] while a limited number of studies have concentrated on the effect of the flow initial ramp, measured by FIR.[6,8,22,23] The flow initial ramp can impact drug–device performance.[24] Although delivered dose is relatively unaffected by flow ramp, total lung dose is more likely to be affected by this parameter, which can be dependent on the formulation and inhaler type. For example, engineered powders (i.e. spray-dried powders) appear to be less susceptible to variation in total lung dose compared to lactose blends and agglomerate formulations.[24] Since low-flow resistance devices require a higher inspiratory airflow rate and effort, a low FIR with this type of devices can adversely impact the dose delivered by increasing oropharyngeal deposition of drug for these latter types of formulations.[24] We can speculate that the lack of difference in FIR values in RS01-L vs. RS01-M in the current study further supports the use of both devices in PAH; however, studies evaluating the powder emptying rate as a function of FIR warrants further investigation to examine the impact on in vitro lung dose delivery efficiency.

Determinants of inspiratory flow and patient's inspiratory maneuver

DPI instructions typically state that, after preparing the device, the patient should breathe out completely while holding the inhaler away from the mouth and not exhale into the device.[25] Disaggregation of particles takes place inside the device before the dose leaves the inhaler[22] and is increased if the acceleration is fast at the start of

Table 5. Correlations between clinical parameters, resting supine hemodynamics, and inspiratory flow pattern with RS01-M in patients with aPAH ($n = 10$).

Variable	Peak inspiratory flow rate, L/min		Inhaled volume, L		Inspiratory effort, KPa		Flow increase rate 20–30, L/s^2	
	r	*p* Values	*r*	*p* Values	*r*	*p* Values	*r*	*p* Values
Age, years	–0.164	0.610	–0.351	0.262	–0.126	0.695	–0.066	0.838
WHO Functional Class	0.133	0.680	–0.528	0.077	0.083	0.7961	0.126	0.695
Pulmonary function test								
FEV_1, % predicted	0.426	0.167	0.485	0.109	0.453	0.138	0.684	0.014
FVC, % predicted	0.332	0.290	0.728	0.007	0.339	0.279	0.567	0.054
FEV_1/FVC	0.558	0.059	–0.188	0.557	0.595	0.041	0.580	0.048
Right heart catheterization								
RAP, mmHg	–0.200	0.532	–0.630	0.027	–0.671	0.016	–0.444	0.147
sPAP, mmHg	0.065	0.838	–0.500	0.097	–0.837	0.0007	–0.710	0.009
dPAP, mmHg	0.065	0.839	–0.437	0.154	–0.775	0.003	–0.633	0.026
mPAP, mmHg	0.024	0.939	–0.464	0.127	–0.793	0.002	–0.667	0.017
PAWP, mmHg	0.529	0.076	–0.309	0.327	–0.212	0.507	–0.311	0.323
TPG, mmHg	–0.108	0.737	–0.371	0.234	–0.713	0.009	–0.566	0.054
PP, mmHg	0.256	0.420	–0.401	0.195	–0.809	0.001	–0.521	0.081
SV, mL	–0.007	0.981	–0.263	0.408	0.234	0.463	0.281	0.374
CO, L/min	0.161	0.616	–0.037	0.907	0.223	0.484	0.368	0.238
CI, L/min/m^2	0.007	0.980	0.001	0.996	0.474	0.118	0.500	0.097
HR, beats/min	0.301	0.340	0.495	0.101	0.177	0.582	0.393	0.205
TPR, WU	–0.104	0.745	–0.373	0.231	–0.655	0.020	–0.662	0.018
PVR, WU	–0.290	0.359	–0.331	0.292	–0.542	0.068	–0.547	0.065
PVC, mL/mm Hg	–0.138	0.668	0.190	0.552	0.810	0.001	0.648	0.022

Note: $p < 0.05$ = statistically significant.

r: Pearson correlation; CI: cardiac index; CO: cardiac output; dPAP: diastolic pulmonary artery pressure; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HR: heart rate; PAWP: pulmonary arterial wedge pressure; PP: pulse pressure; PVC: pulmonary vascular compliance; PVR: pulmonary vascular resistance; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; SV: stroke volume; TPG: transpulmonary gradient; TPR: total pulmonary resistance; WHO: World Health Organization; mPAP: mean pulmonary arterial pressure.

inhalation. Thus, patients should be instructed to inhale "forcefully from the beginning of inhalation."[17] Simple instructions for patients are to breathe in "fast and hard and until lungs are full."[25] Our population was universally instructed to use the device according to the aforementioned recommendations.

Correlation of clinical parameters with inspiratory flow pattern in PAH

Similar to others, we observed a lower PIF or Insp Eff with increasing age with the low resistance device.[3,26] The fact that age could adversely impact a patient's ability to generate an adequate inspiratory flow is concerning; however, despite this observation, our population was able to reach optimal PIF irrespective of age.

Previous reports have found different correlations of inspiratory profile with spirometry.[3,11] In our study, FEV_1 correlated only with Inh V in both devices, and FIR in RS01-L. On the other hand, and in contrast to previous observations in COPD and asthma,[3,26,27] we did not observe any association between FEV_1 and PIF. The lack of consensus about the association of FEV1 and FEV1/FVC with inspiratory profile supports the idea that the selection of device resistance in a specific population should not be made only based on the assessment of these parameters.

In the overall population, FIR correlated with sPAP, mPAP, TPG, and PVC when using RS01-L. Although a similar trend was observed with RS01-M, in our study only PVC was associated with Insp Eff. The association of PVC, an early marker of pulmonary vascular remodeling,[28] with FIR and its potential contributory role to the inspiratory profile in PAH could be relevant for device selection and deserves further investigation.

In our study, there was a clearly different inspiratory flow pattern when the iPAH and aPAH groups were analyzed separately. When comparing the overall inspiratory flow pattern in patients with iPAH and aPAH, only Inh V was different in RS01-L (Fig. 4). It is well known that Inh V is inversely correlated with device resistance.[29] However, whether or not the higher Inh V observed with RS01-L in our study is relevant to DPI performance in aPAH remains unclear.

In aPAH, FIR and Insp Eff strongly correlated with hemodynamics, being more evident in RS01-L; while in iPAH only PIF was associated with diastolic PAP, mPAP,

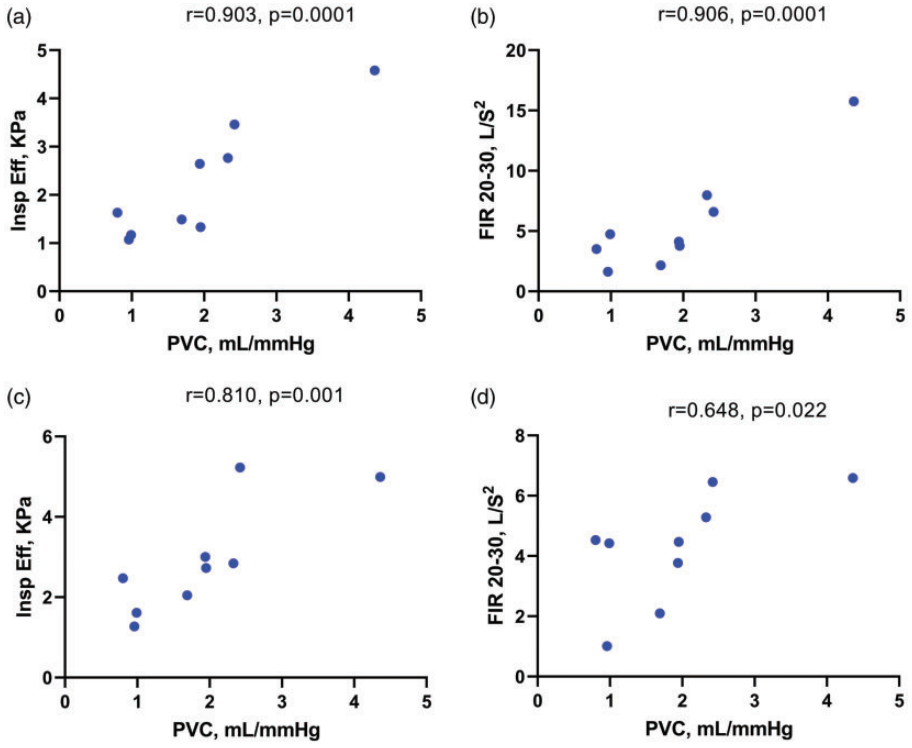

Fig. 5. Correlations between resting supine hemodynamics and inspiratory flow pattern in aPAH. (a) RS01-L inspiratory effort correlated with PVC; (b) RS01-L flow increase rate correlated with PVC; (c) RS01-M inspiratory effort correlated with PVC; and (d) RS01-M flow increase rate correlated with PVC.
Insp Eff: inspiratory effort; FIR: flow increase rate; PVC: pulmonary vascular compliance.

and TPG. Considering the increased attention to the contributory role of FIR for efficient drug delivery to the lungs, our findings might suggest that the aPAH subgroup could potentially experience greater benefit with the use of a medium-resistance vs. a low resistance device to ensure a better PIF and initial inspiratory ramp. However, this hypothesis may be contingent on the aerosol properties of particular drug formulations under study.

Limitations

Our study was limited by a small sample size; therefore, the results should be interpreted with caution. In addition, some prior studies measured PIF without resistance during standard spirometry[30] or through different devices and diseases,[3,26] therefore our findings cannot be directly compared to them. We did not assess patient preference for a particular device, which could also be useful in device selection in patients with PAH. Inspiratory pressure, an important determinant of the patient's ability to generate sufficient flow for optimal DPI use,[10] was not measured in our study.

Our population sub-groups were similar in historic spirometric parameters; however, considering that half of our population had connective tissue disease and that interstitial lung disease is a common manifestation in this group of patients,[31] sub-clinical abnormalities cannot be ruled out.[32] In this regard, mild interstitial lung changes were observed in 60% of aPAH patients in our study. Whether these underlying changes led to physiologic abnormalities responsible for the distinctive pattern observed when hemodynamics were correlated to inspiratory flow in the aPAH sub-group deserves further investigation.

Use of the low- and medium-resistance RS01 DPI devices allowed adequate inspiratory flow in PAH patients; however, the impact of the PIF (or Insp Effs) in our population deserves further investigation and is possibly dependent on particular drug formulations, i.e. micronized blend versus engineered particles.

We observed high variability in PIF across our study population. PIF can be influenced by age, sex, height, weight, Insp Eff and technique, and device resistance. Furthermore, low resistance devices might lead to improper (excessive) PIF.[33] We can speculate that, taken together, these factors might lead to high interindividual variations in PIF in our study population; however, this finding deserves further research.

Our findings should encourage the design of studies in PAH that provide a realistic assessment of the performance of the DPI in this population.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Lawrence S. Zisman is employed by Gossamer Bio, Inc.

Guarantor

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Author contributions

Study design and conception (M.F.-U., L.S.Z., A.B.W.); acquisition, analysis and interpretation of data (M.F.U., K.T.U., L.L., L. S.Z., A.B.W.); drafting and critical revisions of the manuscript (M. F.U., K.T.U., L.L., L.S.Z., A.B.W.); and obtaining funding and administrative support (L.S.Z., A.B.W.).

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Supplemental material

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