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Minimal Inspiratory Flow from Dry Powder Inhalers According to a Biphasic Model of Pressure vs. Flow Relationship

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Inhalation therapy using the dry powder inhaler (DPI) is now the first choice for obstructive pulmonary diseases. We previously measured relationships between inspiratory pressure (P_I) and flow rate of almost all of the DPIs available in Japan, and described an importance of inspiratory efforts. In the present study, we further analyzed the data obtained in the previous study. Although there were linear relationships between P_I and flow^2, the slope became steeper when P_I was less than a certain value (critical P_I, existed between 15–20 cmH_2O). When P_I was less than critical P_I, linear rather than parabolic regression between P_I and flow yielded better fits ($r > 0.90$, $p < 0.001$). Inspiratory flows at the critical P_I were 53.9 (Diskus), 65.8 (Diskhaler), 45.9 (Turbuhaler for Pulmincort), 48.6 (Turbuhaler for Symbicort) and 38.0 l/min (Twisthaler). These findings suggested that flow through the DPI becomes laminar rather than turbulent flow in the range below critical P_Is. We suggest that patients should inhale from the DPIs with inspiratory pressure higher than critical P_I.

Key words: inhalation therapy, bronchial asthma, COPD, rheology

INTRODUCTION

Recently, inhaled steroids combined with long acting beta-stimulants are commonly prescribed for treatment of bronchial asthma and chronic obstructive pulmonary disease [1, 2]. These inhaled drugs may be beneficial to the patients with comorbid cardiovascular diseases to avoid sympathomimetic adverse effects. Many of the currently used inhaled drugs are dry powder formulation which is inhaled by patient's inspiratory flow. For optimal delivery of dry powders to the smaller bronchi, proper use of the DPI devices and suitable inhalation flow rates are both important. However, although many papers about instruction of DPI usage have been published [3, 4], little attention has been paid to inspiratory flow from the DPI. Previously, we have measured relationship between inspiratory pressure (P_I) and inspiratory flow rate (flow) of almost all the DPI devices available in Japan [5], and found parabolic relationships between P_I and flow. However, by further analyzing the data, it seemed that flow was always smaller than predicted value when P_I was small. Therefore, in the present study, we precisely analyzed data in that study again to provide more suitable model of P_I vs flow relationship.

METHOD AND DATA

The data analyzed in the present study was P_I and flow from the five devices, i.e., Diskus, Diskhaler, Turbuhaler for Pulmincort (Turbuhaler-P), Turbuhaler for Symbicort (Turbuhaler-S), and Twisthaler, obtained in the previous study [5]. The method has been described in the previous paper [5]. In brief, as shown in Fig. 1, we set each DPI in a tightly sealed box, and applied several levels of negative pressure to the mouthpiece. A pneumotachometer was fixed to another end of the sealed box. We obtained P_I and flow relationship of individual DPIs with this setting.

Fig. 2 shows the data from Twisthalers. There is an extremely good linear relationship between flow^2 and P_I (Fig. 2A). We have confirmed all the DIPs have such extremely linear relationships [5]. However, it is also seen that the data points located below the regression line (dashed line) in the range below a certain P_I (critical P_I). This finding is more prominent when the data was expressed as flow vs. P_I relationship (parabolic model) (Fig. 2B). In rheological consideration, linear increases in flow^2 with P_I increments suggest that the flow passing through the DPI is turbulent. In the low P_I range this relationship disappeared, and it suggests that turbulent flow no more developed. We hypothesized that the flow assumed another condition, i.e. laminar flow, in this range. If such assumption is true, the flow instead of flow^2 may linearly increase with P_I increments.

Therefore, in the present study, we fitted P_I vs. flow with a linear model in low flow range and did with a parabolic model in high flow range (biphasic model).

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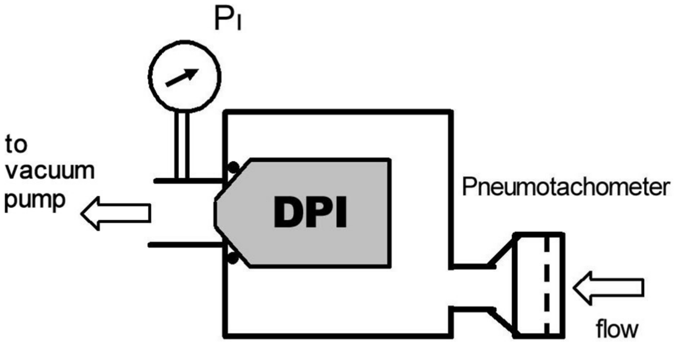

Fig. 1 The device was a tightly sealed box. A negative pressure was applied to one hole and a pneumotachometer was fixed to another hole. DPI: dry powder inhaler, P_I : inspiratory pressure.

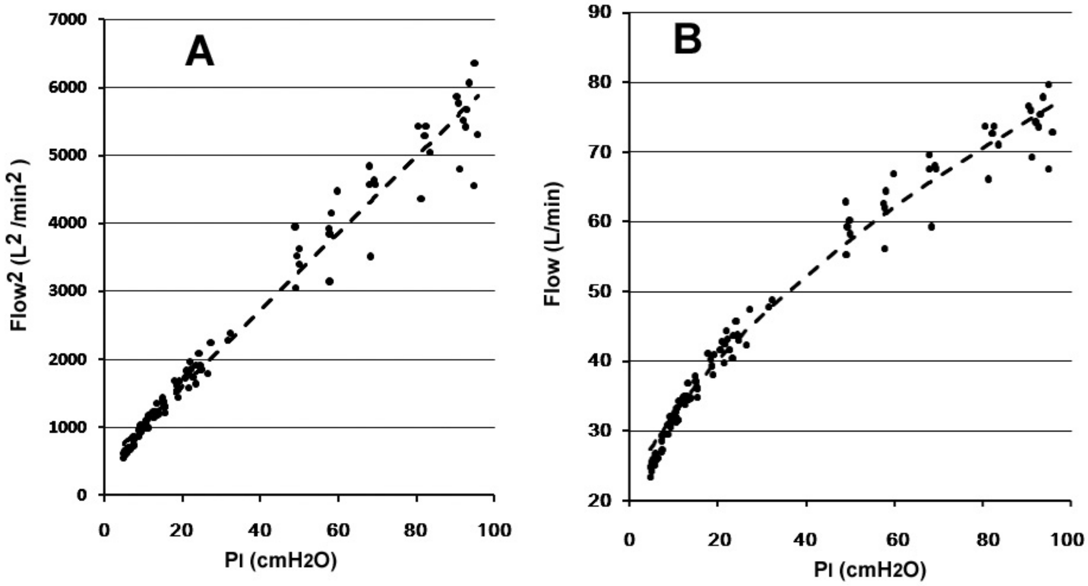

Fig. 2 Examples of P_I vs. flow^2 relationship (A) and P_I vs. flow relationship (B) of Twisthalers. All the flow points scatter below the regression curve (dashed curve) in the rage below a certain P_I.
P_I : inspiratory pressure.

RESULTS

In all the DPIs the flow was smaller than the predicted value when P_I was smaller than a certain P_I (critical P_I). Critical P_Is of Diskus and Diskhaler were approximately 17.5 cmH_2O, and those of Turbuhaler-P, Turbuhaler-S and Twisthaler were approximately 15 cmH_2O. Thus, we temporarily decided lower P_I range as 0–20.5 cmH_2O and higher one as 15.0–100 cmH_2O for Diskus and Diskhaler, and as 0–18.0 cmH_2O and 12.0–100 cmH_2O for Turbuhaler-P, Turbuhaler-S and Twisthaler. We drew a regression line for P_I vs. flow in lower P_I rage, and another regression line for P_I vs. flow^2 in higher P_I range for each DPIs. The intercept point of the two regression curves was regarded to be a critical P_I. Then we calculated parameters of two regression lines, i.e., those for P_I vs. flow (lower P_I rage) and P_I vs. flow^2 (higher P_I range). The results are shown in Table 1.

Fig. 3 shows the regression curves for Twisthalers based on the two models (parabolic model and biphasic model). One can see that the regression curve based on the biphasic model (solid curve) fits better than the parabolic model (dashed curve).

All the regression curves either in the lower or higher P_I ranges had extremely high r (> 0.90) and low p (< 0.001) values in any of DPIs. Table 1 shows parameters of these regression lines or curves. In the low pressure range it was expressed as "flow = a x P_I + b", and in the high pressure range it was "flow^2 = a x P_I +b". Critical P_I and the flow at the critical P_I are also shown in Table 1. To express fitness of the regression curves to the data points, we defined a parameter S. S at low pressure range was expressed as Sl, and that at high pressure range was named as Sh.

$S = \sqrt{(\sum(\text{real Yi} - \text{predicted Yi})^2/(n - 2)}$

Where real Yi is a flow value at P_I = i, and predicted Yi is corresponding flow on the regression line. n is a sample number. If "real Yi − predicted Y" distributed with a normal distribution, S means the standard deviation to the linear regression line.

In any of the devices, Sl of the biphasic model was always smaller than that of the parabolic model, and Sh of the biphasic model was also smaller than that of the parabolic model. Thus, it can be said that the regression curves in the present study fitted better than

Table 1 Parameters of linear regression lines expressed as y = a x +b, and critical P_I and critical flow. Turbuhaler-P: Turbuhaler for Pulmincort, Turbuhaler-S: Turbuhaler for Symbicort. n is sample number of each devices. $S = \sqrt{(\sum (\text{real } Yi - \text{predicted } Yi)^2/(n-2))}$., Sl, Sat low pressure range. Sh, S at high pressure range.

device	n	Parameters of regression curves: Low pressure range a	b	Sl	High pressure range a	b	Sh	Critical pressure (cmH_2O)	Critical Flow (l/min)	Parameters of regression curves in the previous analysis a	b	Sl	Sh
Diskus	5	1.99	25.5	4.47	120.7	1188.0	1165	14.3	53.9	126.0	872.2	5.09	1171
Diskhaler	3	2.19	25.7	1.41	156.1	1480.0	566	18.3	65.8	167.0	780.4	3.07	639
Turbuhaler-P	5	1.32	22.7	1.51	77.3	751.4	339	17.6	45.9	79.3	626.8	1.84	357
Turbuhaler-S	4	1.36	24.4	1.18	87.1	812.0	383	17.8	48.6	89.0	688.3	2.00	400
Twisthaler	5	1.19	19.4	1.07	54.8	585.8	373	15.6	38.0	56.4	478.7	1.75	382

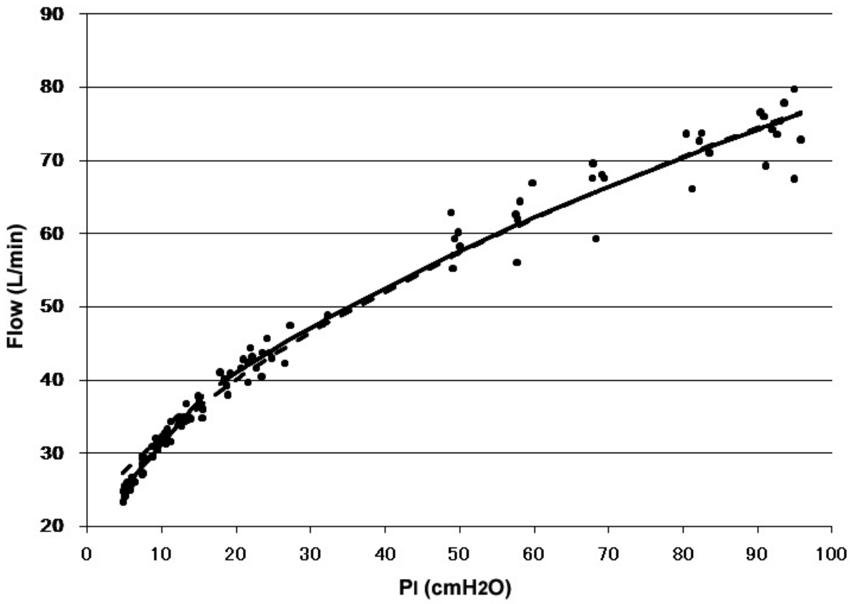

Fig. 3 Comparison of the P_I - flow regression curves based on a parabolic model (dashed curve) and a biphasic model (solid curve) of Twisthalers.

those in the previous study.

Fig. 4A shows flow vs. P_I prediction curves of all the DPIs based on the biphasic model. Comparing with the parabolic model (Fig. 4B) [5], newly calculated prediction curves had apparent inflection points.

DISCUSSION

Although many studies concerning instruction of the DPI usage have been published [3, 4], little attention has been paid to inspiratory flow from the DPI. As is known, inspiratory flow is a critical factor for delivering dry powders to the airways using the DPI systems [6, 7]. Although many papers about minimal flow rates for effective drug delivery from DPIs have been published [6–8], usually patients can perceive level of their inspiratory efforts rather than flow rates. Thus, for instruction of optimal inspiratory flow, it is necessary to know relationship between inspiratory efforts and flow rates through individual DPIs. We have shown a graph presenting this relationship in the previous paper (Fig. 4B) [5]. By using that graph, the physician can instruct optimal efforts to inhale from each DPI. For example, to instruct inspiration at 40 l/min through Twisthaler, “inspire with an effort to drink orange juice using *20 cm length* straw” may be easy to understand.

Most of the DPIs contain a mechanism which disperses powdered drug to be fine particles. Owing to this mechanism, fine particle drugs are effectively delivered to the distal, as well as proximal, airways. All the DPIs analyzed here generate fine particles by turbulent flow in the inspiratory channel. In the previous study we assumed that inspiratory flow was turbulent in entire flow range. However, in rheological considerations, turbulent flow no more develops when flow becomes low. If this is true, dispersion of powdered drug may decrease in low flow range. In the present study, we have reviewed the data in the previous report [5], and found that exact flow rates were always smaller than predicted ones at low P_I (i.e. low flow) range. The present study revealed that linear regression more excellently fit to the P_I-flow data in the low flow range, suggesting that inspiratory flow became laminar rather than turbulent in that range.

The critical flows, at which turbulent flow became linear, of large channel DPIs were 53.9 l/min for

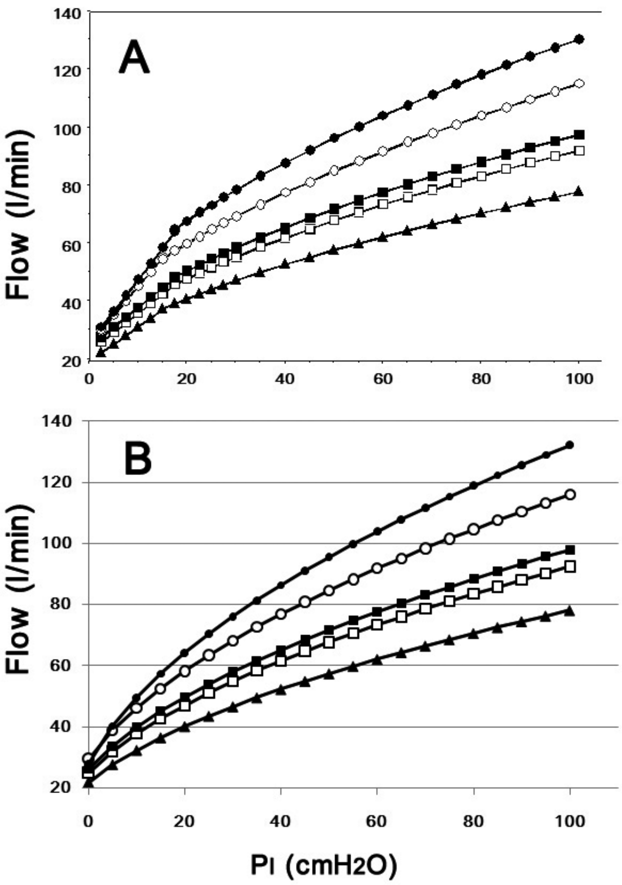

Fig. 4 Simulated P_I vs. flow relationships of all DPIs based on parameters shown in Table 1. A: curves based on a biphasic model. B: curves based on a parabolic model (5).
●: Diskhaler, ○: Diskus, ■: Tubuhaler for Symbicort, □: Turbuhaler for Pulmicort, ▲: Twisthaler,

Diskus and 65.8 l/min for Diskhaler. The critical flow for Diskus was higher than the minimum flow rate for drug dispersion reported by Prime *et al.* (30 l/min) [7] or Hill *et al.* (30 L/min) [9], but near to that reported by Palander *et al.* (60 L/min) [8]. The critical flow for Diskhaler was between the minimum flows reported by Srichana *et al.* (30 l/min) [10] and Prime *et al.* (90 l/min) [7]. On the other hand, the critical flow of small channel DPIs were less than those for large channel DPIs. They were 45.9 l/min (Turbuhaler-P), 48.6 l/min (Turbuhaler-S), 38.0 l/min (Twisthaler). Crtical flow for Turbuhalers (-P and -S) were smaller than the minimal inspiratory flow for drug emission reported by Palander *et al.* (60/ l/min) [9] or Tarsin *et al.* (60-90 l/min) [6]. The critical flow for Twisthaler was higher than minimal flow by Yang *et al.* (~30 l/min) [11]. Therefore, critical flow rates determined here were generally slightly higher than minimal inspiratory flows determined by drug dispersion. Presumably in low P_I range, turbulent flow still exited in inspiratory channel but it gradually disappeared while P_I became smaller. We speculate that when the patient inhales from DPI with flow less than critical flow, only small amount of fine particles may be generated and delivery to the small airways may become less. Therefore, this study suggests that both large channel DPIs (Diskus and Diskhaler) and narrow channel devices should be inhaled with inspiratory pressure higher than 15-18 cmH_2O. Considering studies those have been reported [6, 9], inspiratory efforts higher than critical P_I may be encouraged for small channel DPIs [5].

In conclusion, further analyses of the data in the previous study suggested that patients should inhale from DPI with efforts higher than critical P_I.

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