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ORIGINAL ARTICLE

Exhalation immediately before inhalation optimizes dry powder inhaler useTetsuri Kondo, MD¹, Makoto Hibino, MD¹, Toshimori Tanigaki, MD², Motoki Ohe, MD¹, and Sakurako Kato, MD³¹Department of Respiratory Medicine, Shonan Fujisawa Tokushukai Hospital, Fujisawa, Kanagawa, Japan, ²Division of Respiratory Medicine, Atsugi Circulation Clinic, Atsugi, Kanagawa, Japan, and ³Department of Respiratory Medicine, Tokai University Oiso Hospital, Kanagawa, Japan**Abstract**

Objective: Although exhalation immediately prior to inhalation (EPI) from dry powder inhalers (DPIs) is universally advised, its benefit has not been investigated. The objective of this study to assess the effects of EPI on inhaled flow from a DPI. **Methods:** We measured peak inhaled flow rate (PIFR) and inhaled gas volume of 25 volunteers unfamiliar with DPIs. They inhaled strongly and deeply through a flow meter either with or without EPI before and after connecting Turbuhaler[®] or Diskus[®]. **Results:** Median PIFR increased significantly with EPI both without connection to DPIs (178.8 versus 140.4 L min⁻¹), and with connection to Diskus[®] (75.6 versus 67.8 L min⁻¹), or to Turbuhaler[®] (51.0 versus 48.0 L min⁻¹). As a result, the number of subjects whose PIFR exceeded 60 L min⁻¹ was significantly increased with connection to either Diskus[®] (76 versus 64%) or to Turbuhaler[®] (24 versus 4%). EPI significantly increased median inhaled volume both without connection to DPIs (2.84 versus 1.84 L), and with connection to Diskus[®] (1.95 versus 1.66 L), or to Turbuhaler[®] (1.86 versus 1.28 L). EPI significantly increased F_{0.2} (flow at 0.2 s after onset of inhalation) and AC₃₀ (flow acceleration at 30 L min⁻¹), parameters representing the rate of flow increase during the early phase of inhalation, in all the three groups. **Conclusions:** EPI increases PIFR which may augment drug dispersion and facilitate fine particle generation from a DPI.

Keywords

Chronic obstructive pulmonary disease, drug delivery, handling, inhalation therapy, peak inspiratory flow

History

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Introduction

Instructions for the use of many DPIs (dry powder inhalers) include exhalation preceding inhalation (EPI) (e.g. http://www.youtube.com/watch?v=PJNowG6_CZo, <http://www.asthma.ca/adults/treatment/turbuhaler.php>, <https://hcp.gsk.co.uk/products/relvar/ellipta/how-to-use.html>). Although the clinical benefit of EPI in pressurized metered dose inhalers has previously been reported [1], the proposed explanation is not applicable to DPIs because DPI use requires rapid inhalation. Therefore, the effect of EPI on flow during inhalation from a DPI requires further consideration. In the present study, we assessed the effects of EPI quantitatively on flow from a DPI.

Methods

This study was permitted by the Ethics Committee of Shonan Fujisawa Tokushukai Hospital. Since instructions concerning inhalation from a DPI are usually given with the patient's initial use of the device, we recruited 25 volunteers unfamiliar with a DPI to simulate those patients. Healthy subjects for the

study were recruited with the assistance of the first healthy subject, also a volunteer, consisting of his friends and acquaintances and screened according to the study criteria outlined. The inclusion criteria were: age >20 years and without currently treated respiratory disease. The exclusion criteria were a cough or dyspnea at the time of the study, tobacco use immediately preceding the study, and current use of a DPI. All the subjects were recruited between 1 May 2013 and 30 September 2013. The subjects were informed of the purpose and method of the study, and participated voluntarily.

We measured the respiratory flow rate of the subjects through a hot-wire flow meter (RF-HE, Minato Medical, Osaka, Japan) with or without a DPI, Turbuhaler[®] or Diskus[®], interspersed (Figure 1). The DPI was stored in a small airtight box to which the flow meter was connected, and flow signals were stored in an analyzing system (PowerLab, Castle Hill, Australia) with a sampling rate of 1.0 kHz. Initially the subject inhaled strongly and forcefully through the pneumotachometer either from end expiration (FRC; functional residual capacity) or from the end of a deep exhalation. Then, the subject inhaled from the DPI either with or without performing EPI with a 15 s interval. This process was repeated two times for each DPI either with or without EPI with a 15 s interval between each maneuver as shown in Figure 1. Thus, the experiment consisted of six sessions with 10 trials. All subjects were encouraged to inhale strongly and

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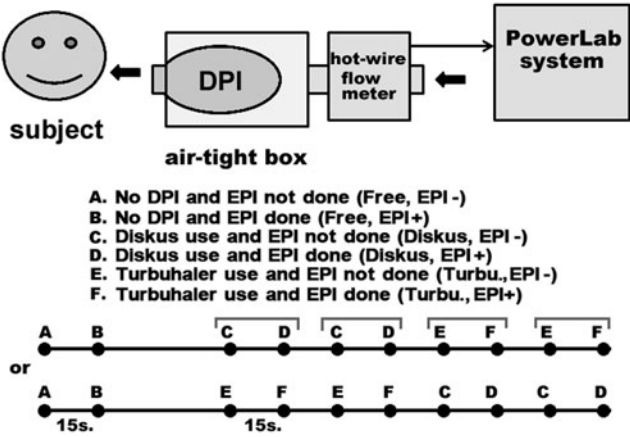


Figure 1. Experimental setup. The subject inhaled from a DPI (dry powder inhaler) stored in a small airtight box to which a hot-wire flow meter was connected (DPI sessions), or directly through the flow meter (DPI free sessions). Flow signals were analyzed with a PowerLab system (PowerLab, Castle Hill, Australia). The experiment consisted of six sessions with 10 trials (each set of trials using a DPI was done two times): no DPI and no EPI (Free and EPI-) or with EPI (Free and EPI+), Diskus use without EPI (Diskus and EPI-) or with EPI (Diskus and EPI+), and Turbuhaler use without EPI (Turbu. and EPI-) or with EPI (Turbu. and EPI+). EPI: exhalation immediately prior to inhalation.

deeply, but the extent of the prior exhalation was not specified.

Since we obtained two sets of data from each DPI, we compared flow patterns of the EPI session for each DPI, and if the flow pattern satisfied the following criteria the set (with and without EPI sessions) was regarded as representative. The selection criteria were as follows: the higher PIFR, the shorter time to reach PIFR, or the steeper initial rise of flow. Volumes of inhalations and exhalations were calculated by integration of surge signals. We further calculated two parameters from the flow signals: $F_{0.2}$ (flow at 0.2 s after onset of inhalation) and AC_{30} (flow acceleration at 30 L min⁻¹). These were assumed to represent the rate of flow increase during the early phase of inhalation from the DPI [2–4].

The data were expressed as median, 75th percentile, and 25th percentile. Data differences of <0.05 using a Wilcoxon signed-rank test (StatView 5.0, SAS Institute, Cary, NC) were considered significant.

Results

Subjects' demographic features are shown in Table 1. In the session without DPIs and without performing EPI, all subjects began inhalation at the end of a normal expiration, i.e. at functional residual capacity (FRC). When exhalation was performed before inhalation from the DPI, the median exhaled gas volume was 0.82 (1.15, 0.55) L (75th percentile and 25th percentile).

Figure 2 shows the peak inhaled flow rates (PIFRs) in each experimental situation. Median PIFR was 140.4 (180.6, 115.8) L min⁻¹ when the DPI was not connected to the flow meter, and it increased significantly to 178.8 (262.8, 134.4) L min⁻¹ by adding the EPI maneuver. With Diskus[®] connection, the median PIFR was 67.8 (78.0, 55.8) L min⁻¹, and by adding EPI, it increased significantly to 75.6 (86.4, 64.8) L min⁻¹. It should be noted that the number of subjects whose

Table 1. Subject details.

Age (mean ± SD, years old)	37.4 ± 11.2
Sex	
Male/female	19/6
Race	
Asian (Japanese)	25
Height (mean ± SD, cm)	169.8 ± 8.3
Smoking	
Never	16
Past	4
Current	5
Comorbidity	
Hx of asthma	2
Allergic rhinitis	2

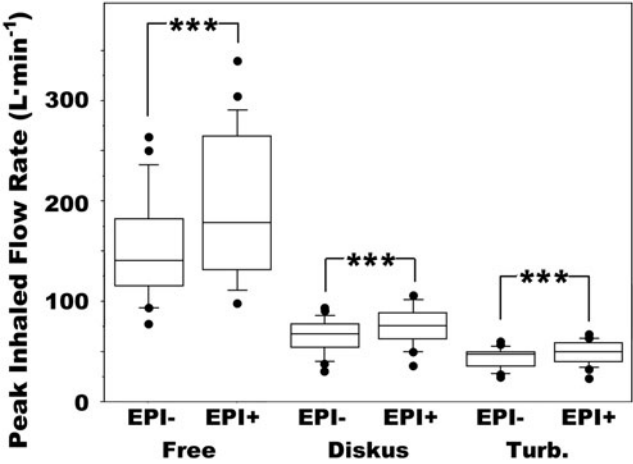


Figure 2. Peak-inhaled flow rates with (EPI+) and without (EPI-) prior exhalation in each experimental situation. Free: without DPI connection, Disk: Diskus[®] connection, and Turbu: Turbuhaler[®] connection. *** $p < 0.0001$.

PIFR was >60 L min⁻¹ was 16 (64%) without EPI, while it increased to 19 (76%) with EPI. With Turbuhaler[®], median PIFR was 48.0 (49.8, 36.0) L min⁻¹ without EPI and it increased significantly to 51.0 (58.2, 41.4) L min⁻¹ with the EPI maneuver. Only one out of 25 subjects (4%) exceeded 60 L min⁻¹ PIFR without EPI, while six subjects (24%) exceeded this flow rate by adding EPI.

The time for inhalation through Diskus[®] increased significantly from 2.49 (2.80, 1.80) s to 2.76 (4.35, 2.04) s by adding EPI. The time through Turbuhaler[®] also increased significantly from 2.94 (3.60, 2.20) s to 3.55 (4.46, 2.24) s with EPI.

Figure 3 shows the inhaled gas volume in each experimental situation. When the DPI was not attached, median inhaled volume without EPI was 1.84 (2.10, 1.56) L and that with EPI was 2.84 (3.12, 1.97) L. The difference of 1.0 L was statistically significant. Median inhaled volume through Diskus[®] without EPI was 1.66 (1.91, 1.19) L and it increased significantly to 1.95 (2.46, 1.38) L with EPI, a difference of 0.29 L. Median inhaled volume through Turbuhaler[®] without EPI was 1.28 (1.65, 0.89) L, and it increased significantly to 1.86 (2.24, 1.13) L with EPI, a difference of 0.58 L.

Figure 4 shows the parameters representing the increase in rate of flow during the early phase of inhalation. As shown in

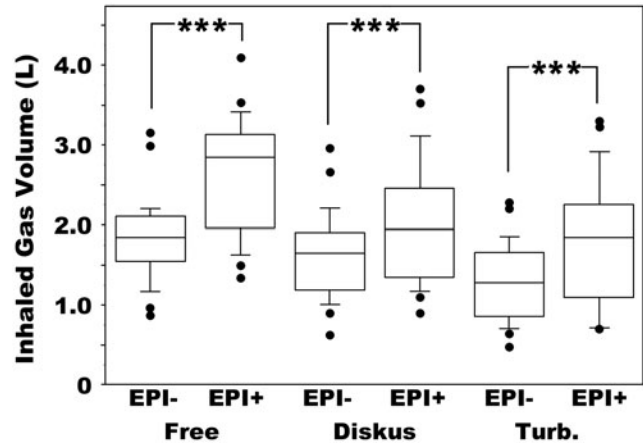


Figure 3. Inhaled gas volumes with (EPI+) and without (EPI-) prior exhalation in each experimental situation. Free: without DPI connection, Disk: Diskus® connection, and Turbu: Turbuhaler® connection. *** $p < 0.0001$.

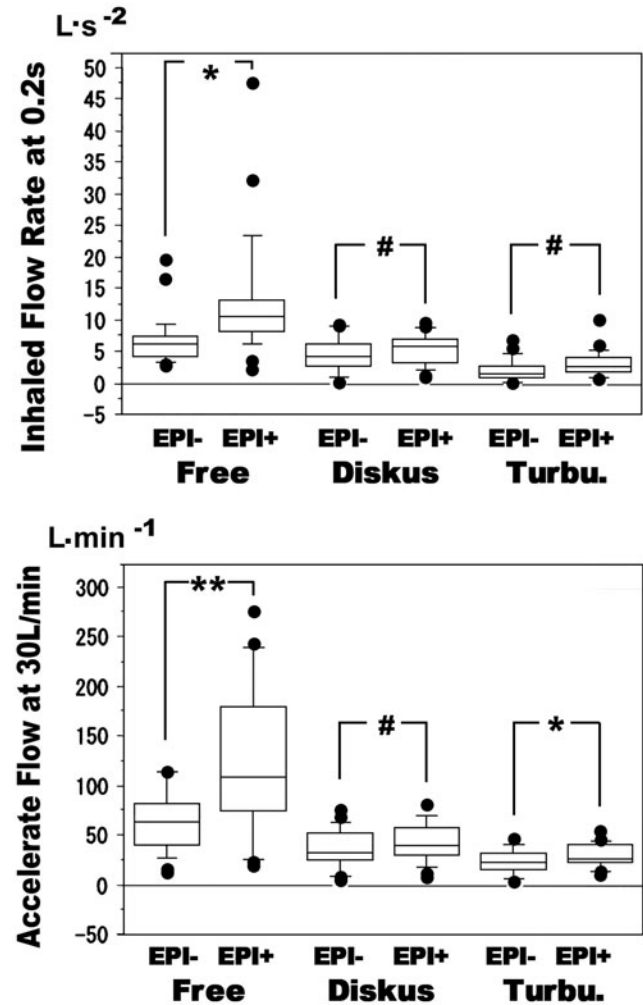


Figure 4. Parameters reflecting rate of flow increase during the early phase of inhalation. Both $F_{0.2}$ (panel A) and AC_{30} (panel B) increased significantly with prior exhalation in all the three experimental situations. *** $p < 0.0005$, * $p < 0.01$, # $p < 0.05$.

Figure 4(A), $F_{0.2}$ increased significantly with EPI in all three experimental conditions. These changes were from 62.9 (81.5, 40.8) to 108.5 (178.8, 73.6) $L \min^{-1}$ (DPI free), from 31.8 (50.9, 25.5) to 39.1 (56.4, 30.8) $L \min^{-1}$ (Diskus®) and from

22.5 (31.7, 15.6) to 27.4 (39.9, 23.3) $L \min^{-1}$ (Turbuhaler®). As shown in Figure 4(B), AC_{30} also increased significantly with EPI in all the three experimental situations. These changes were from 6.18 (7.43, 4.28) to 10.43 (13.03, 8.33) $L \min^{-2}$ (DPI free), from 4.18 (6.12, 2.66) to 5.91 (6.99, 3.37) $L \min^{-2}$ (Diskus®) and from 1.73 (2.72, 0.97) to 2.65 (4.14, 1.91) $L \min^{-2}$ (Turbuhaler®). Table 2 summarizes the results of these experiments.

Discussion

Drug particles contained in DPIs are dispersed by patients' inhaled air flow. Optimally this requires a flow rate higher than 30 or 60 $L \min^{-1}$ either from Diskus® or Turbuhaler® [5–7]. Usually this flow rate is not sufficient to generate fine particles capable of arriving at the lower airways which usually requires a flow rate higher than 60 $L \min^{-1}$ [5–7]. Although many patients with bronchial asthma or COPD can generate sufficient inhaled flow from Diskus® and Turbuhaler® [8–10], some fail to do so [11–13]. Therefore, instruction concerning proper inhalation technique for DPIs is critically important.

In the present study, mean PIFR through Diskus® was higher than 60 $L \min^{-1}$ without the EPI maneuver, but 36% of the subjects failed to do so. In the Turbuhaler® study without EPI, only one of the 25 subjects inhaled with PIFR >60 $L \min^{-1}$. When EPI was used with Diskus®, the median PIFR was increased by 7.8 $L \min^{-1}$, and the number of subjects who inhaled with suboptimal flow was decreased by 12%. With Turbuhaler® use, although EPI increased median PIFR by only 3.0 $L \min^{-1}$, the number of subjects with an appropriate inhalation flow rate rose to six patients (24%). Thus, EPI increases the likelihood of an appropriate PIFR in subjects unfamiliar with DPIs.

It is known that a blister or reservoir type DPI such as Diskus® or Turbuhaler® requires a high flow rate during the early phase of inhalation. Bisgaard et al. [2] reported that the mean time to peak of the aerosol cloud from the Diskus® was 0.16 ± 0.14 s, and that from the Turbuhaler® was 0.19 ± 0.03 s. Inhalation flow at 0.2 s should be higher than that for drug dispersion, i.e. >30 $L \min^{-1}$. When EPI was not performed, median $F_{0.2}$ exceeded 30 $L \min^{-1}$ in Diskus® use, while it did not reach 30 $L \min^{-1}$ in Turbuhaler® use. EPI raised $F_{0.2}$ significantly with both types of DPI use, and median $F_{0.2}$ exceeded 30 $L \min^{-1}$ in Turbuhaler® use. We calculated AC_{30} as well [4] because accelerated flow is one of the strong determinants of energy of the dispersed particles. AC_{30} also increased significantly with EPI in all the three experimental situations. Therefore, our results suggest that EPI may facilitate drug dispersion both by augmenting flow rate and by accelerating flow during the early phase of inhalation.

We previously reported that a considerable number of subjects unfamiliar with DPIs, were not able to attain sufficient PIFR even after verbal instructions [14]. Although some equipment such as In-Check® or other inspiratory flow trainers may be useful in this regard, their effects have some limitations [11] and this equipment may not be available in some clinics throughout the world. Since EPI is an easy and effective maneuver, this

Table 2. Summary of the results (median, 75th, and 25th percentiles).

	DPI free		Diskus® connection		Turbuhaler® connection	
	without EPI	with EPI	without EPI	with EPI	with EPI	with EPI
PIFR (L min ⁻¹)	140.4 (180.6, 115.8)	178.8*** (262.8, 134.4)	67.8 (78.0, 55.8)	75.6*** (86.4, 64.8)	48.0 (49.8, 36.0)	51.0*** (58.2, 41.4)
Inhaled volume (L)	1.84 (2.10, 1.56)	2.84*** (3.12, 1.97)	1.66 (1.91, 1.19)	1.95*** (2.46, 1.38)	1.28 (1.65, 0.89)	1.86*** (2.24, 1.13)
F _{0.2} (L min ⁻¹)	62.9 (81.5, 40.8)	108.5** (178.8, 73.6)	31.8 (50.9, 25.5)	39.1# (56.4, 30.8)	22.5 (31.7, 15.6)	27.4# (39.9, 23.3)
AC ₃₀ (L min ⁻²)	6.18 (7.43, 4.28)	10.43** (13.03, 8.33)	4.18 (6.12, 2.66)	5.91# (6.99, 3.37)	1.73 (2.72, 0.97)	2.65* (4.14, 1.91)
Inhalation time through DPI (s)			2.49 (2.80, 1.80)	2.76** (4.35, 2.04)	2.94 (3.60, 2.20)	3.55** (4.46, 2.24)

****p* < 0.0001, ***p* < 0.0005, **p* < 0.01, #*p* < 0.05 (compared with values of corresponding no EPI trials in the same set).

should always be done in blister- or reservoir-type DPI use.

In the present study, EPI increased inhaled gas volume as well, and the median increases were 0.29 L for Diskus® and 0.58 L for Turbuhaler®, respectively. Thus with EPI the subject started inhalation at a lung volume lower than FRC using part of the expiratory reserve volume (ERV). As expected, an increase in inhaled gas volume is associated with a significant increase in inhalation time. Long inhalation time is mandatory for drug dispersion in the use of capsule DPIs, but its role is unclear in blister DPIs [15]. Although prolongation of the time passing through turbulent channels in the DPI may facilitate smaller particle generation, prolongation of the time reaching the peak dispersion may be a considerable disadvantage. However, protracted inhalation might enhance drug deposition in the airways. Studies concerning these issues are lacking. From these considerations, the implications of lung volume and inhalation time changes produced by EPI remain to be elucidated.

The EPI-induced increase in PIFR can be explained by length-tension relationship of the inspiratory muscles. On one hand, median PIFR through Diskus®, which has a low resistance channel, increased from 67.8 to 75.6 L min⁻¹ with EPI. On the other hand, median PIFR through Turbuhaler®, which has a high resistance channel, increased from 48.0 to 51.0 L min⁻¹. The efforts (or mouth or airway pressure) required to generate these flow changes are calculated from flow-pressure relationship of individual devices [16,17], and they are almost the same value (~1 kPa). Windisch et al. [18] reported that maximal inspiratory mouth pressure at a residual volume is 1–2 kPa higher than that at FRC. When no instruction was given, our subjects inhaled from FRC, and they inhaled from a level between RV and FRC in the EPI session. Since the difference between RV and FRC, i.e. ERV, is ~1.6 L in healthy humans, the subjects may have started inhalation at lung levels approximately 0.8 L lower than FRC in the EPI session, and this maneuver enhanced inspiratory mouth pressure by 1 kPa. The pressure versus flow relationship in each device in the present study is consistent with that described in the previous studies [16,17]. The previously calculated increment in PIFR as a result of a 1 kPa increment of driving pressure is similar to the results of our present study. That is, PIFR was increased by 7.8 L min⁻¹ from 67.8 L min⁻¹ in the low resistance device (Diskus®) and by 3.0 L min⁻¹ from 48.0 L min⁻¹ in Turbuhaler® in the high resistance device (Turbuhaler®) secondary to a 1 kPa increment of driving pressure.

The results of the present study were obtained on normal healthy subjects. Our observations may also be valid in those with controlled asthma because their pulmonary mechanics are unchanged. Although EPI may also ameliorate the DPI inhalation profile in patients with chronic obstructive pulmonary disease (COPD) or uncontrolled asthma, lung inflation in patients with these conditions may be associated with changes in maximal inspiratory mouth pressure and ERV which may alter the results obtained.

Conclusions

EPI significantly increases PIFR and inhaled volume with DPI use while accelerating flow in the early phase of inhalation. As a result, EPI may augment drug dispersion and facilitate fine particle generation from a DPI.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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