In Vitro Evaluation of Aerosol Performance and Delivery Efficiency During Mechanical Ventilation Between Soft Mist Inhaler and Pressurized Metered-Dose Inhaler

Wei-Ren Ke, Wei-Jhen Wang, Tzu-Hsuan Lin, Chao-Ling Wu, Sheng-Hsiu Huang, Huey-Dong Wu, and Chih-Chieh Chen

BACKGROUND: Soft mist inhalers (SMIs) generate aerosols with a smaller particle size than pressurized metered-dose inhalers (pMDIs). However, the whole-span particle size distribution (PSD) of SMIs and the optimal delivery method of SMIs during mechanical ventilation have not been fully investigated. This study aimed to measure the PSD of the SMI alone and the SMI coupled to an inhalation aid (eg, a spacer, a valved holding chamber), as well as the delivery efficiency of SMI in different actuation timings and circuit positions during mechanical ventilation. As a suitable comparison, the pMDI was chosen for the same measurement. METHODS: SMIs (2.5 μg/actuation of tiotropium) were compared with pMDIs (100 μg/actuation of salbutamol). A microorifice uniform deposit impactor was utilized for the particle sizing of drug aerosols generated by inhalers alone, inhalers with a spacer, and inhalers with a valved holding chamber. To optimize the delivery efficiency of both inhalers during mechanical ventilation, the operating parameters included the circuit positions and actuation timings in the ventilator circuit. Particle sizes and inhaled doses were measured with an optical particle sizer and filters used to collect and quantify the drug, respectively. RESULTS: The SMI generated a smaller mass medium aerodynamic diameter (MMAD) than that from the pMDI. The extrafine-particle fraction (EFPF, < 1 μm) of the SMI was significantly higher than that of the pMDI. With the use of either inhalation aid, the MMAD of both inhalers decreased, and both inhalers with inhalation aid showed significant increases in EFPF. During mechanical ventilation, the optimum way to deliver the SMI and pMDI was at 15 cm from the Y-piece and actuated at the end of expiration and the onset of inspiration, respectively. CONCLUSIONS: The SMI with an inhalation aid showed marginal improvement on the PSD. The inhaler type, actuation timing, and position within the circuit also played important roles in delivery efficiency during mechanical ventilation. *Key words: soft mist inhaler; metered-dose inhaler; inhalation aid; particle size distribution; mechanical ventilation; inhaled dose*. [Respir Care 2020;65(7):1001–1010. © 2020 Daedalus Enterprises]

Introduction

Soft mist inhalers (SMIs) are a new generation of metered-dose inhaler that share the advantages of pressurized metered-dose inhalers (pMDIs) and are characterized as easy to operate and easy to coordinate inhalers.[1] They do not necessitate the use of a propellant, pneumatic, or electrical power source to generate aerosols, using instead the mechanical force from a compressed spring. Once the spring is released, the energy forces the metered volume of drug solution through 2 nozzles. The 2 jets of solution are

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generated and converge at a specific angle. The resulting impaction of the 2 jets generates the slow-moving mist aerosol.[2,3] Aerosols generated by SMIs emit much more slowly and for a longer time than do aerosols generated by pMDIs.[4-6] Previous studies have revealed that the longer spray duration reduces the problem of hand-breath incoordination, making it easier for users to achieve the correct therapy technique.[7,8] The differences in spray duration and velocity between SMIs and pMDIs result from different aerosol-generation mechanisms. The driving force in the pMDI is propellant, and the vapor pressure of propellant in the canister is the primary factor that effects the spray velocity of aerosols.[9,10]

The particle size of aerosols is a dominant factor in determining the drug deposition patterns in the human lung. During a normal breathing pattern, the particles in the size range of 1–5 μm tend to be delivered to the peripheral lung region; particles $>$ 10 μm easily deposit in the upper airway, and those in the size range of 0.1–1 μm tend to be exhaled from human lung. For particles $<$ 0.1 μm, deposition fractions increase with decreasing particle size, and diffusion becomes the main deposition mechanism due to Brownian motion.[11-13] Conventionally, the fine-particle fraction (FPF), ie, the mass fraction of particle size $<$ 5 μm, is a parameter correlated to peripheral lung deposition. However, the FPF also includes the extra-fine particles ($<$ 1 μm), which have a different deposition tendency compared to micron-sized particles.[14,15] Thus, when interpreting inhaler performance with FPF, it is important to take into account the particle size distribution (PSD). Previous research has noted that SMIs can generate drug aerosols with a mass median aerodynamic diameter (MMAD) $<$ 5 μm and an FPF $>$ 60%.[2,16-18]

Moreover, because inhalation aids such as a spacer or a valved holding chamber (VHC) can improve the PSD and hand-breath coordination, pMDIs are recommended to be used along with an inhalation aid.[19,20] As for SMIs, studies have reported that drug delivery from an SMI with a VHC reduces fine particle masses, and the literature advises against the use of inhalation aids with an SMI for adults and older children.[17,21-23] However, other studies suggest that an inhalation aid is needed for children $\leq$ 5 y old and patients who are unable to coordinate.[24,25] Wachtel and colleagues[17] used the next-generation impactor at flow of 30 L/min to measure the PSD of SMIs alone or coupled to a VHC under pediatric and adult flows. They reported that the FPFs of the SMI alone and the SMI with a VHC were 63% and 51%, respectively, and there were approximately 25% and 20% of label dose, respectively, deposited at the microorifice collector, which captures particles with $<$ 0.54 μm in size.[17] The aerosols captured at the microorifice collector belong to the size range of particles that tend to be exhaled; therefore, the high proportion of this particle fraction generated with an SMI suggests that the normal breathing pattern may not be suitable for receiving SMI aerosols. Thus, measuring the whole span of PSD generated from an SMI alone and from an SMI with an inhalation aid is important to understand the particle deposition tendency in the human lung.

In critical care, aerosol medicines are commonly administered to intubated patients receiving mechanical ventilation. Aerosol delivery efficiency during mechanical ventilation depends on several variables, such as humidity, aerosol generators, device position in the circuit, and ventilator parameters.[26-28] Jet nebulizers, vibrating mesh nebulizers, and pMDIs have been widely studied for use in mechanical ventilation. Delivery methods for the usage of SMIs in an intubated patient model have been found in only a few studies because delivering an effective performance of SMIs during mechanical ventilation provides a challenging scenario.[29,30] Because the SMI itself is not sealed, connecting SMIs in the ventilator circuit without any modification or inclusion of

QUICK LOOK

Current knowledge

Previous studies have reported that soft mist inhalers (SMIs) generate smaller particle sizes with a higher fine-particle fraction (FPF), ie, $<$ 5 μm, than pressurized metered-dose inhalers (pMDIs). FPF is a parameter correlated to peripheral lung deposition. However, the FPF also includes extra-fine particles (EFPF), ie, $<$ 1 μm, which have a different deposition tendency compared to micron-sized particles. Thus, when interpreting inhaler performance, it is important to take into account the range of the particle size distribution.

What this paper contributes to our knowledge

The SMI generated a bimodal particle size distribution with a smaller mass median aerodynamic diameter and higher FPF than the pMDI. In comparing the EFPF, the fraction from the SMI was significantly higher than the pMDI. Use of an SMI with an inhalation aid showed marginal improvement on the particle size distribution. Furthermore, in an in vitro adult ventilator model, the optimum way to deliver the SMI and pMDI was 15 cm from the Y-piece and actuated at the end of expiration and the onset of inspiration, respectively.

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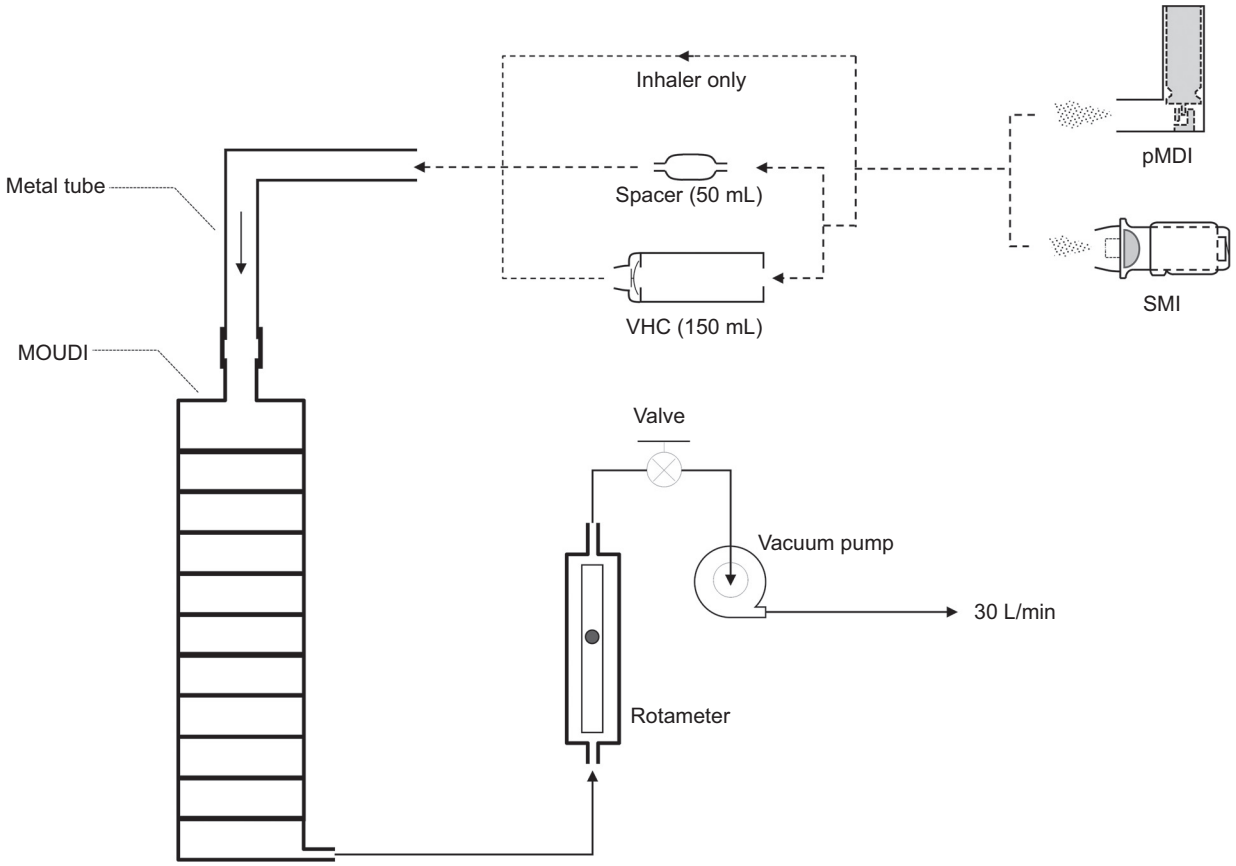

Fig. 1. The experimental system for the measurement of aerosol size distribution through 3 different delivery methods. MOUDI = microorifice uniform deposit impactor; VHC = valved holding chamber; SMI = soft mist inhaler; pMDI = pressurized metered-dose inhaler.

an adapter could lead to leakage, which may cause life-threatening complications in ventilator-dependent patients. Suggett and Nagel[30] assessed the delivery efficiency of SMIs connected by a RespiConnect adapter between the inspiratory limb and the Y-piece during mechanical ventilation, and approximately 30% of the labeled dose could be delivered to the distal end of the endotracheal tube (ETT). However, there is no recommended way to utilize SMIs during mechanical ventilation, and the SMI adapter is not available in every country. It is unsafe to use SMIs without any modification or an adapter in the ventilator circuit.

In this study, the whole span of aerodynamic PSD generated from SMIs alone and with inhalation aids (ie, a spacer and a VHC) was profiled (0.056–18 μm) with a microorifice uniform-deposit impactor (MOUDI) at flow of 30 L/min. In addition, to optimize the delivery efficiency of SMIs in a model of adult mechanical ventilation, the operating parameters included the circuit positions and actuation timings in the non-humidified ventilator circuit. As a suitable comparison, a hydrofluoroalkane pMDI underwent equivalent measurement conditions.

Methods

Inhaler Types

Two types of inhalers were chosen for research: the SMI (tiotropium, labeled dose of 2.5 μg/actuation) and the pMDI (salbutamol, labeled dose of 100 μg/actuation), which uses hydrofluoroalkane 134a as a propellant.

PSD Measurement

The test system was set up as shown in Figure 1. Three drug delivery methods for both inhalers were investigated: the inhaler alone, the inhaler with a spacer, and the inhaler with a VHC. Each parameter was tested in triplicate. An induction port (ie, a metal tube) was connected between the outlet of the inhalation device and a MOUDI (Model 110, MSP, Minneapolis, Minnesota). A cascade impactor was used for the aerodynamic particle sizing of aerosol particles emitted from the inhalers. Particle cut-off diameters of MOUDI at suction flow of 30 L/min were 0.056, 0.10, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6, 10, and 18 μm. Mylar filters (47 mm) were used as collection media. Drug deposited

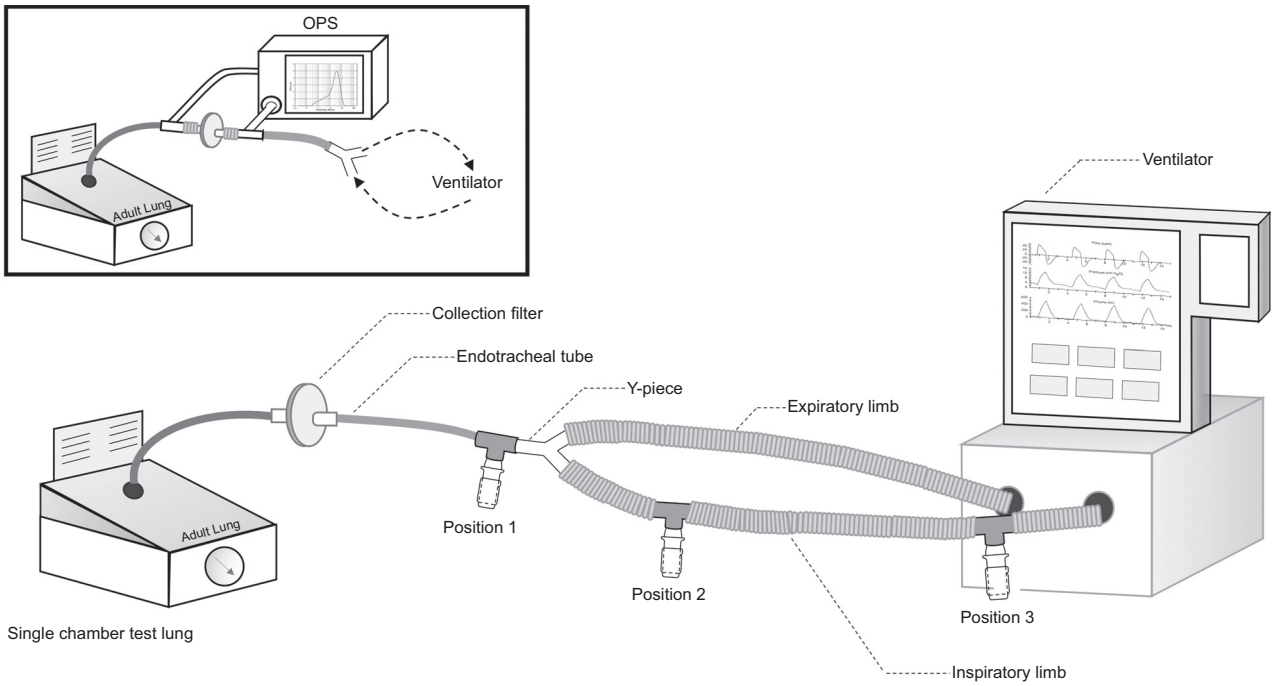

Fig. 2. The in vitro model of adult mechanical ventilation for the measurement of delivery efficiency through 3 inhaler positions. OPS = optical particle sizer.

on the filters was measured via spectrophotometry. The MMAD, geometric standard deviation (GSD), and 2 mass fractions, the FPF (ie, the mass fraction of particle size < 5 μm) and the EFPF (ie, the mass fraction of particles < 1 μm), were defined by the following equations.

$$\text{MMAD} = 50\text{th percentile size } (d_{50\%}) \quad [1]$$

$$\text{GSD} = \left(\frac{d_{84\%}}{d_{16\%}}\right)^{1/2} \quad [2]$$

$$\text{FPF} = \frac{\text{the mass} < 5\ \mu\text{m}}{\text{the total mass in impactor}} \times 100\% \quad [3]$$

$$\text{EFPF} = \frac{\text{the mass} < 1\ \mu\text{m}}{\text{the total mass in impactor}} \times 100\% \quad [4]$$

Aerosol Drug Delivery during Mechanical Ventilation

Figure 2 shows a schematic diagram of the in vitro model of adult mechanical ventilation adopted from the work of Ari et al.[26] A PB-840 ventilator (Puritan Bennett, Minneapolis, Minnesota) was operated in volume-controlled ventilation mode with the adult settings. Ventilator settings were tidal volume = 500 mL, breathing frequency = 15 breaths/min, inspiratory time = 0.9 s, peak inspiratory flow = 60 L/min, PEEP = 5 cm H_2O, ramp flow pattern and oxygen concentration = 21%. A 120-cm ventilator circuit was connected to the test lung (resistance = 5 cm H_2O/L/s, compliance = 0.1 L/cm H_2O) via a 7.5-mm inner-diameter ETT. A filter was positioned distal to the ETT to measure the inhaled dose. The volumetric median diameter (VMD) of the aerosols was measured using an optical particle sizer (Model 3330, TSI, St Paul, Minnesota) placed between the filter and the end of the ETT. An optical particle sizer measures the PSD in the size range of 0.3–10 μm with a sampling flow of 1 L/min. To maintain the same flow in the ventilation circuit, the 1-L/min filtered flow exhausted from the optical particle sizer was drained back to the system. Inhaled doses and VMDs were measured separately.

The pMDI with a spacer was used to deliver the aerosol drug during mechanical ventilation, and the SMI was attached to the ventilator circuit with a T-piece adapter. However, there are 2 sites of air leakage in the structure of SMIs: one at the mouthpiece air vents, and the other between the dosing chamber casing and the inside of the mouthpiece. Preliminary work has noted that if both sites of air leakage are not sealed, SMI operation with the ventilator will fail. Thus, in our study, the mouthpiece air vents were sealed with a silicon adapter, and the air leakage at the dosing chamber casing was sealed with an O-ring.

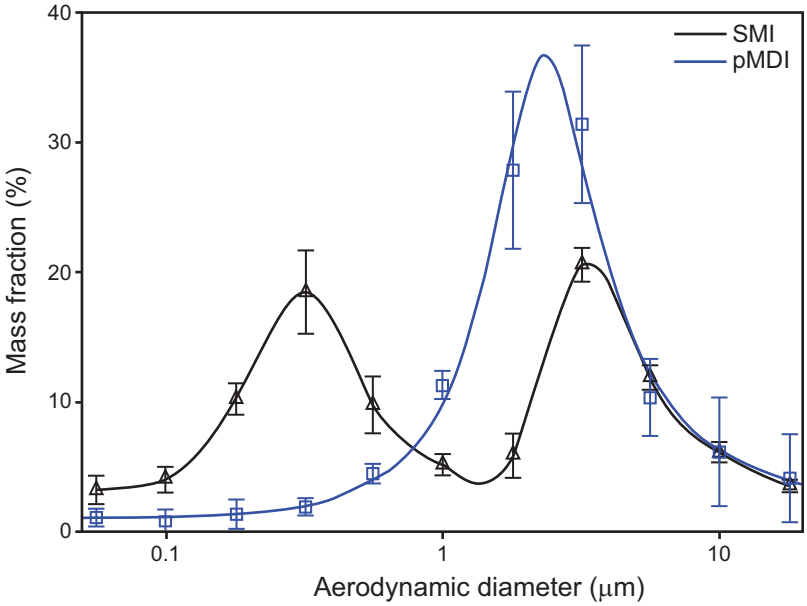

Fig. 3. Particle size distributions of emitted aerosols from the SMI and pMDI alone. Lines connect points representing mean mass fractions of 3 replicates, and error bars represent 1 SD of the mean. SMI = soft mist inhaler; pMDI = pressurized metered-dose inhaler.

The 2 operating parameters included the timing of actuation and the placement of inhaler in the nonhumidified ventilator circuit. For the evaluation of the actuation timing, each inhaler was tested in 3 different actuation timings, including the onset of inspiration (T1), the onset of expiration (T2), and the end of expiration (T3). For the evaluation of the inhaler placement in the ventilator circuit, both inhalers were actuated at 3 different positions, including between the ETT and the Y-piece (P1), the inspiratory limb at 15 cm from the Y-piece (P2), and 15 cm from the ventilator (P3). Eight actuations were introduced into the ventilator circuit with 1-min intervals between each actuation for each trial, and each parameter was tested in triplicate.

Data Analysis

The amount of drug deposited in the filters was eluted with distilled water after each trial. The eluted drug was measured via spectrophotometry (UV-1800, Shimadzu, Kyoto, Japan) at the wavelength of 237 nm and 276 nm for tiotropium and salbutamol, respectively. All statistical calculations of MMAD, GSD, FPF, EFPF, and inhaled dose were analyzed with analysis of variance. A $P < .05$ was considered statistically significant.

Results

In this study, the MOUDI collected and fractionated drug aerosol by aerodynamic diameter through serial stages of impaction to evaluate the PSD, as shown in Figure 3 and Figure 4. For the salbutamol pMDI alone, the unimodal PSD with a MMAD of 3.40 ± 0.44 μm and a GSD of 2.72 ± 0.37 was measured. As for the tiotropium SMI, a bimodal PSD with a coarse-particle mode at 3.2 μm, a fine-particle mode at 0.32 μm (MMAD = 1.51 ± 0.70 μm; GSD = 5.04 ± 0.08). When the SMI with each inhalation aid was delivered through the MOUDI impactor, the aerosol generated insignificantly smaller MMAD (SMI alone: 1.51 ± 0.70 μm, SMI + spacer: 0.94 ± 0.14 μm; SMI + VHC: 0.66 ± 0.11 μm, $P = .12$) than the SMI alone. In contrast, the MMAD showed a significant decrease with each inhalation aid on pMDI (pMDI alone: 3.40 ± 0.44 μm; pMDI + spacer: 2.53 ± 0.10 μm; pMDI + VHC: 2.30 ± 0.27 μm, $P = .01$).

The FPFs and EFPFs of each inhaler with 3 different delivery methods are summarized in Figure 5. For aerosols emitting from inhaler alone, there was no significant difference in the FPF of the delivered dose between the SMI and pMDI (SMI: 73.3 ± 0.9%; pMDI: 71.8 ± 9.1%, $P = .78$). When it comes to comparisons of the EFPF, the fraction of the SMI was significantly higher than that of the pMDI (SMI: 46.8 ± 3.0%; pMDI: 9.5 ± 2.4%, $P < .001$). Furthermore, although the FPF (SMI alone: 73.3 ± 0.9%; SMI + spacer: 75.8 ± 1.3%; SMI + VHC: 81.6 ± 1.4%, $P = .11$) generated from the SMI alone was marginally less than the SMI delivered with each inhalation aid, the EFPF (SMI alone: 46.8 ± 3.0%; SMI + spacer: 53.0 ± 3.2%; SMI + VHC: 61.2 ± 1.1%, $P < .001$) showed a significant increase. The FPF values for the pMDI with a

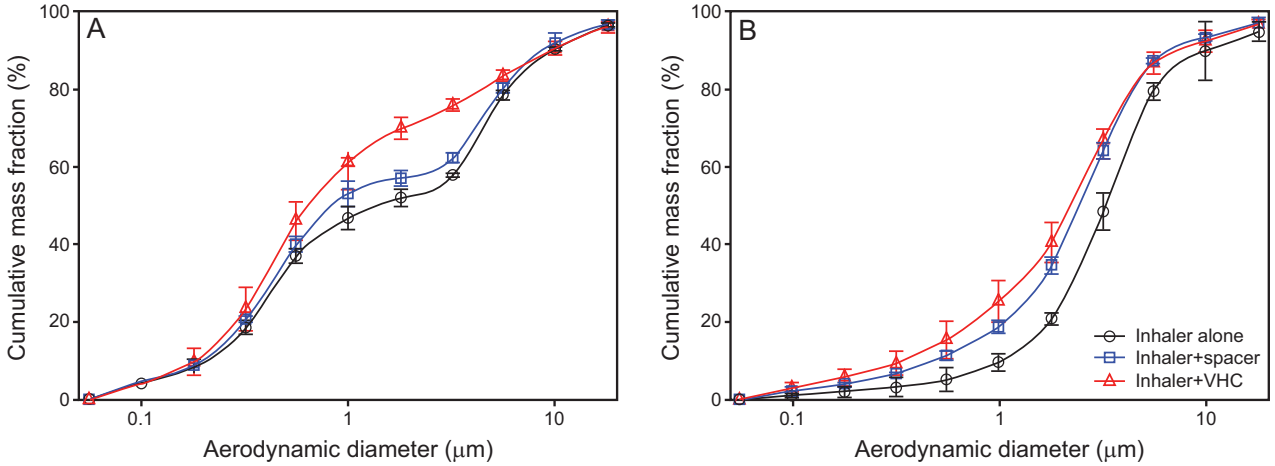

Fig. 4. Cumulative mass distributions of emitted aerosols from (A) the soft mist inhalers and (B) the pressurized metered-dose inhalers through 3 different delivery methods. Lines connect points representing mean cumulative mass fractions of 3 replicates, and error bars represent 1 SD of the mean. VHC = valved holding chamber.

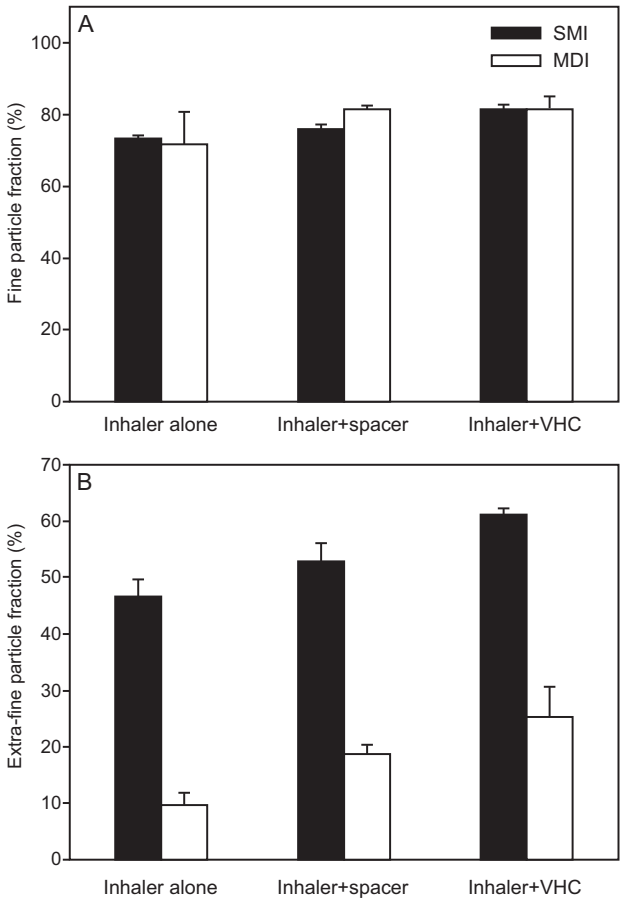

Fig. 5. (A) Fine-particle fraction (< 5 μm) and (B) extra-fine-particle fraction (< 1 μm) achieved with the SMI and the pMDI with 3 different delivery methods. Each bar height represents the mean of 3 replicates, and error bars represent 1 SD. VHC = valved holding chamber; SMI = soft mist inhaler; pMDI = pressurized metered-dose inhaler.

spacer and the pMDI with a VHC were 81.6 ± 0.9% and 81.7 ± 3.3% (P = .12), respectively, and the EFPF increased significantly (pMDI alone: 9.5 ± 2.4%, pMDI + spacer: 18.7 ± 1.6%; pMDI + VHC: 25.3 ± 5.3%, P < .001).

Inhaled doses and VMDs for each inhaler at 3 different positions in the ventilator circuit is shown in Figure 6. SMIs (P1: 12.2 ± 4.2%; P2: 22.9 ± 5.8; P3: 5.4 ± 2.4, P = 0.01) and pMDIs (P1: 9.6 ± 2.5%; P2: 26.1 ± 2.0; P3: 1.0 ± 0.7, P < .001) delivered the highest inhaled doses at P2 and the least efficient at P3 in the nonhumidified ventilator circuit.

Figure 7 reveals the effect of different actuation timings on inhaled doses and VMDs emitted from each inhaler at P2 during mechanical ventilator. The pMDI with spacer performed the best when actuated at the onset of inspiration (T1: 26.1 ± 2.0%; T2: 11.3 ± 5.4; T3: 9.0 ± 2.0, P < .001), and there was no significant difference in VMD among 3 actuating timings (P = .22). As for SMI, it delivered the greatest amount of drug when actuated at the end of expiration (T1: 9.7 ± 1.8%; T2: 11.9 ± 4.5; T3: 22.9 ± 5.8, P = .02), and VMD appeared insignificantly different among 3 actuating timings (P = .19).

Discussion

When evaluating the inhaler performance, FPF and MMAD should not be the only indicator; the whole range of PSDs and other indicators (eg, spray velocity and spray duration) should also be considered. These indicators may also help respiratory therapists or clinicians to choose an appropriate inhaler and inhalation aid for patients. In this study, the MOUDI impactor was used to measure the PSD of inhalers alone, inhalers with a spacer, and inhalers with a VHC. The results showed that, although the SMI generated

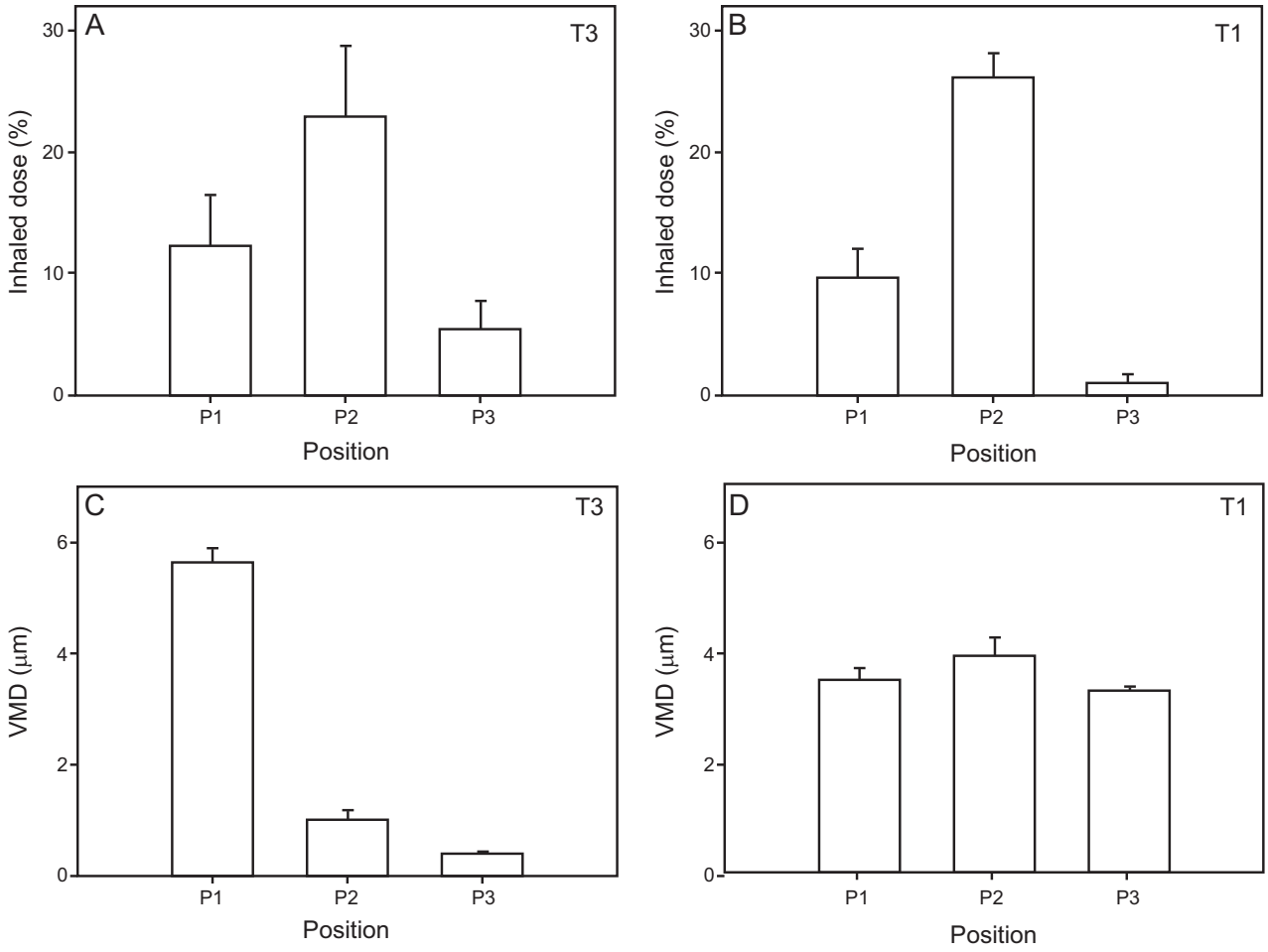

Fig. 6. The effect of the inhaler placement in ventilator circuit on drug delivery efficiency: (A) inhaled doses and (C) VMD emitted from the soft mist inhaler at the end of expiration; (B) inhaled doses and (D) VMD emitted from the pressurized metered-dose inhaler at the onset of inhalation. Each bar height represents the mean of 3 replicates and an error bar represents 1 SD. VMD = volumetric median diameter.

smaller MMAD than the pMDI, the PSD of the SMI showed bimodal distribution and the EFPF of the SMI dominated approximately half of the SMI-emitted particles. We speculated that the bimodal distribution might be attributed to the formation of satellite droplets during the impaction process of converging jets. The break of fluid filaments led to an array of uniformly spaced large droplets (known as main drops) with smaller satellite droplets in between.[31] Furthermore, previous research reported larger MMADs than those measured in our study.[16-18] It is inferred that impactors used in previous research were not able to measure the range of PSD in SMI aerosols; Wachtel et al[17] also noted that approximately one quarter of the SMI label dose was collected at the microorifice collector (cut-off diameter: 0.54 μm) of the next-generation impactor at a flow of 30 L/min. In contrast, the MOUDI impactor utilized in our study can measure the particle size down to 0.056 μm and revealed the PSD of SMI aerosols $<$ 0.54 μm. Because extra-fine particle distribution generated from the SMI was detected, the MMAD shifted to the smaller diameter. Moreover, it is conventionally believed that aerosol particles $<$ 1 μm tend to be exhaled.[12,13] Thus, although SMIs generate aerosols with high FPF, the high content of EFPF would have a greater chance to be exhaled during a normal breathing pattern. Breath-holding after inhalation could be a better way to receive more SMI aerosol because the breath-hold technique enhances the deposition fraction of extra-fine aerosols in the human lung by increasing the time for sedimentation.[12,20] Brand and colleagues[8] reported that delivered doses improved from 37% to 53% by training patients to inhale SMI aerosols with a deep breath and breath-hold technique.

Generally, using an inhalation aid helps patients improve hand–breath coordination. Apart from this, increasing the distance between the sampler (or patients) and the inhaler by using an inhalation aid not only increases the resident time for the aerosol cloud to dry out but also reduces aerosol velocity.[32-34] According to our preliminary work, the

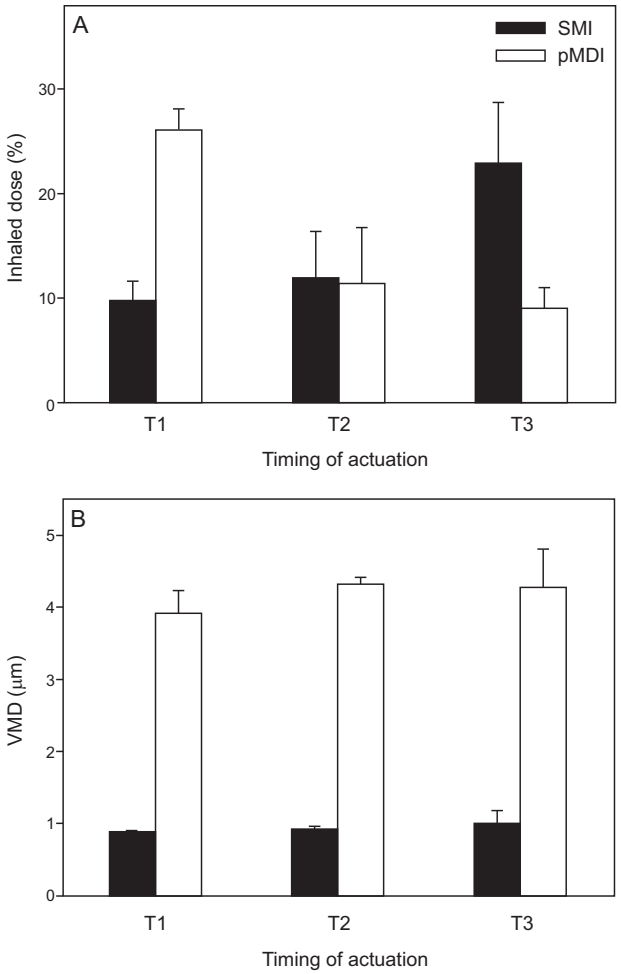

Fig. 7. The effect of actuation timing emitted from the soft mist inhaler and the pressurized metered-dose inhaler during mechanical ventilation on (A) inhaled dose and (B) volumetric median diameter. Each bar height represents the mean of 3 replicates and an error bar represents 1 SD. SMI = soft mist inhaler; pMDI = pressurized metered-dose inhaler; VMD = volumetric median diameter.

spray velocity of both inhalers was recorded with a high-speed camera (i-Speed 2, iX-Cameras, Rochford, Essex, United Kingdom). The mean spray velocity at a distance of 8 cm from the pMDI was 11 times faster than that from the SMI (pMDI: 14.2 ± 3.23 m/s; SMI: 1.32 ± 0.07 m/s; data not shown). Thus, due to larger particles and higher velocity emitted from pMDIs, adding an inhalation aid on pMDIs was more efficient in improving hand-breath coordination and PSD than using an inhalation aid on SMIs. In contrast, as a result of a great amount of extra-fine particles and low spray velocity generated from the SMI, the use of an inhalation aid showed marginal improvement on the PSD.

According to our understanding, there is no consensus on how to deliver SMI aerosols during mechanical ventilation. Delivery position in the ventilator circuit and the actuation timing play important roles in determining how much inhaled dose and what median size of drug aerosol is delivered to the distal end of the ETT. To measure the inhaled doses and VMDs for each inhaler during mechanical ventilation, we compared 3 different positions in the ventilator circuit and 3 different actuation timings for each inhaler. Both inhalers delivered the highest inhaled dose at 15 cm from the Y-piece and the smallest inhaled dose at 15 cm from the ventilator. In addition, VMD was the smallest at P3 for both inhalers and appeared to significantly increase when placed at P1 for SMIs. When placed at P3, drug aerosols passed through a longer distance to reach the collection filter. The longer the pass length is, the lower the aerosol penetration and the smaller the VMD will be.[32] Furthermore, P1 has less inhaled dose than that at P2. Aerosols emitted from the SMI at P1 may not have been thoroughly dried. Because the aerosols instantly encountered the tubing contraction between the T-piece and the ETT, Ari et al[26] speculated that turbulence occurs at the contraction and contributes to particle loss.

For the actuation timing, the pMDI delivered the highest inhaled dose when actuated at the onset of inspiration during mechanical ventilation. Due to the short spray duration of pMDI, the actuation of pMDIs at the onset of inspiration would decrease in time for aerosol to settle in the ventilator circuit. Even if pMDIs were actuated at the end of expiration, inhaled doses profoundly decreased during mechanical ventilation. Thus, to maximize inhaled doses, it is crucial for pMDI usage to synchronize with the onset of inspiratory flow in the ventilator circuit.[33-35] Moreover, the optimal delivery of the SMI was at the end of expiration. Our preliminary work with a high-speed camera noted that the spray duration of the tiotropium SMI was 8.4 times longer than that of the salbutamol pMDI (SMI: 1.43 ± 0.12 s; pMDI: 0.17 ± 0.03 s, data not shown). Because the spray duration of pMDI was much shorter than the inspiratory time, pMDI synchronized with the onset of inspiration resulted in higher drug delivery efficiency than actuation during expiration.[36] When the SMI was actuated at the onset of inspiration, approximately one third the drug aerosol was retained in the ventilator circuit and was not delivered to the patient until the next inspiratory phase. During the waiting period, the drug aerosol gradually settled in the tubing. To reduce retention of the SMI aerosols in the circuit during expiration, actuating SMIs at the end of expiration proved to be the most efficient way to deliver SMI drug.

Limitations

Due to the drug limitation, we chose different bronchodilators for each inhaler. The results do not represent all SMI and pMDI bronchodilators because different drug formulations have different aerosol properties. Another limitation of this study was that only 2 inhalation aids were tested.

Our results may not be generalizable to other devices because each inhalation aid has its own structure, which may lead to different outcomes. Moreover, our study used the MOUDI impactor set at a constant flow to measure aerosol size distributions on inhaler alone and inhalers with an inhalation aid. Additional in vitro and in vivo correlation studies are needed to confirm our findings. Finally, we only tested 1 set of representative ventilatory parameters to simulate mechanical ventilation for the adult and did not apply a humidifier in the ventilator circuit. Further studies are needed in a wider range of ventilator settings and applying humidifier.

Conclusions

The SMI is a new generation of metered-dose inhaler that does not use propellant. In this study, we described the in vitro characteristics of SMIs and pMDIs. For the PSD, the SMI shows a bimodal distribution with small MMAD and high FPF. With the use of either inhalation aid (spacer or VHC), the MMAD of both inhalers decreases. From the aspect of aerosol particle size, the SMI is not recommended to be used with an inhalation aid due to the low MMAD and high EFPF, which means that SMI aerosols tend to be exhaled under normal-breathing pattern. Finally, we noted that actuation timing and position in the circuit play an important role in delivery efficiency during mechanical ventilation. Our findings suggest that the optimal way to deliver SMIs and pMDIs in a ventilator circuit is to place the inhalation device at 15 cm from Y-piece, and to actuate at the end of expiration for SMIs and the onset of inspiration for pMDIs. Further in vivo studies are needed to evaluate the clinical relevance of our findings.

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