

Effect of Nebulizer Breath-Guiding on Breathing Patterns

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Summary

The investigation evaluates a novel breath-guiding concept implemented into the eFlow Integrated Nebulizer, aiming at optimised drug delivery efficiency by improving patients' breathing patterns. Vibrating mesh nebulizers, especially when breath-triggered, are favoured for maximizing dose delivery—an essential attribute for costly biopharmaceuticals. However, their prolonged nebulization times can hinder patient adherence. Among other means, the breath-guiding approach, incorporating both, device-based and app-based feedback, aims to resolve this contradiction by promoting deeper and slower breathing. In an investigation involving 64 participants (healthy, obstructive, and restrictive lung disease patients), three nebulizer variants were evaluated. Flow metrics were recorded over ~4 minutes per variant and analysed using median-averaged breathing curves. Multifactorial analysis of variance (ANOVA) revealed a significant effect of the device on key breathing pattern parameters. Compared to the eFlow OS, the eFlow Integrated with breath-guiding consistently ensured maximum inspiratory flow rates to be below 30 L/min, which reduces drug deposition in the upper airways. It also resulted in prolonged breath duration and increased I/E ratios enhancing drug delivery efficiency and shortening overall treatment time. The use of the breath guide app increased tidal volume, prolonged inspiration time and could work as an educational tool, promoting adherence and correct inhalation technique. The investigation also illustrates that breathing patterns across participant groups differ substantially from standard US Pharmacopeia (USP) patterns, demonstrating deficiencies in using those for realistic nebulizer performance testing and reference for breath-guiding evaluations.

Key Message

The use of increased direction-dependent breathing resistance, visual and haptic feedback as well as an app, can significantly alter the breathing pattern of users resulting in optimised deposition and reduced nebulization times.

Introduction

Modern nebulization technologies have evolved significantly, and vibrating mesh nebulizers have become prominent due to their efficiency and ability to deliver precisely high doses of medication with minimal losses. Especially for innovative drug formulations – very often biopharmaceuticals, efficiency gets even more important due to its high drug costs. This is one reason why breath-triggered nebulizers are gaining more and more interest and are the state-of-the-art technology today: they provide high delivered doses, sometimes above 90 %. On the other hand, breath-triggered devices very often come with long nebulization times since aerosol is only generated during part of the inspiration phase. This is critical considering the impact of nebulization time on patients' adherence, acceptance of the therapy and quality of life [1] [2]. Concepts are needed to resolve this contradiction. Besides high mesh output rate and high efficiency in terms of delivered dose, the optimisation of the breathing pattern is a key factor to reach short nebulization times and therefore patient adherence. Studies also show that longer inspiration times and slower inspiratory flow rates enhance drug deposition in the lungs and therefore therapeutic outcome, as they allow more time for aerosol particles to settle deep in the airways and prevent deposition in the upper airways [3] [4]. Additionally, increased inspiration to expiration ratio (I/E) prolongs the time of aerosol production which increases mean device output per breath. At the same time, it also has a positive effect on deposition efficiency and therefore therapeutic outcomes. Conversely, inappropriate breathing techniques may lead to suboptimal drug delivery. Today immense effort is required to educate patients using the inhalation device correctly [5]. In the context of patient-centric product development, the device should guide the patient during inhalation towards an improved breathing pattern. In those cases, standard USP breathing patterns used for performance testing are not suitable anymore, as they neglect the effect of this improved breathing resulting from breath-guiding. Therefore, device specific breathing patterns need to be generated. Recently researchers and nebulizer suppliers have begun exploring breathing patterns that more closely reflect real-life respiration. However, these patterns are either artificially constructed or derived from a limited pool of healthy subjects [6] [7] [8].

The aim of this paper is to quantify the effect of breath-guiding on the patient's breathing and to demonstrate the deficiency of testing with standard USP breathing patterns. Therefore, 64 participants, both healthy and with respiratory conditions, were recruited for the investigation and their breathing

patterns were recorded using three nebulizer variants. The data were analysed with respect to tidal volume, inspiratory peak flow rate as well as I/E ratio, and results were compared across the devices.

Methods

We recruited healthy subjects and patients with obstructive and restrictive lung diseases (Table 1). Participants were eligible if ≥ 18 years of age and if they gave their informed consent.

Table 1: Participants of the investigation

Variable/Group	Healthy	Obstructive	Restrictive	Total
Indications		Asthma, COPD, cystic fibrosis, bronchiectasis	Pulmonary fibrosis, sarcoidosis	
N	25	24	15	64
Mean Age	41.12 $\pm$ 11.31	50.67 $\pm$ 17.64	60.73 $\pm$ 11.46	49.30 $\pm$ 15.81
Mean Height (cm)	175.4 $\pm$ 7.17	171.88 $\pm$ 8.66	168 $\pm$ 7.96	172.34 $\pm$ 8.33
Mean Weight (kg)	72.68 $\pm$ 12.04	69.46 $\pm$ 16.82	72.4 $\pm$ 12.59	71.41 $\pm$ 14.00

Three PARI nebulizer variants were used in the investigation (Figure 1): One eFlow Open System (eFlow OS) and two variants of the eFlow Integrated [9]. Guiding at the device only was achieved by a built-in resistance (Figure 2) as well as haptic and visual feedback which indicated flow rates above 30 L/min. The PARI Breath Guide® App (v0.11-1) allowed additional feedback (exceeded flow rate warning, live flow rate curve and guiding towards increased tidal volumes via animation [9]). With the low resistance of the eFlow OS the corresponding breathing pattern is expected to be similar to normal breathing and therefore serves as a reference. All participants inhaled approximately 4 minutes through each of the 3 nebulizer variants with a nose clip (without aerosol production). Besides breathing through the nebulizers, participants answered a questionnaire involving a multi-option Likert scale about it.

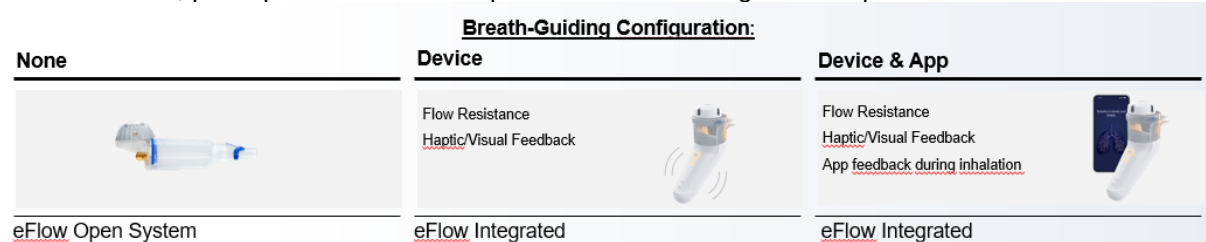


Figure 1: Nebulizer variants used in the investigation

Breathing patterns were recorded via a Sensirion SFM3300 flow rate sensor placed between the device and the participant. During the measurements an average of 48.1 ± 5.7 breathing cycles were recorded for each participant and subsequently phase averaged using the median of the family of curves. For the phase averaging, the flow rate data was split at each positive zero crossing and normalized to the average breath duration. Then, median averaging of the curves was performed, resulting in the red curve in Figure 3. Via integration of the flow curves, the breathing volume was extracted. From these median averaged curves, among others the following parameters were extracted and analysed: duration of inspiration, expiration and breathing cycle, I/E ratio, breathing frequency, maximum flow rate, tidal volume.

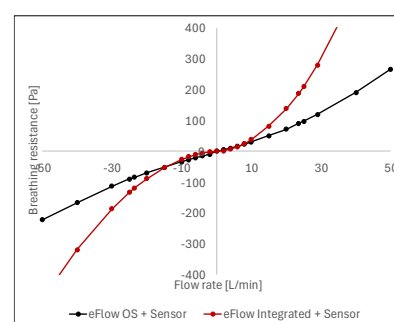


Figure 2: Breathing resistance of the two devices

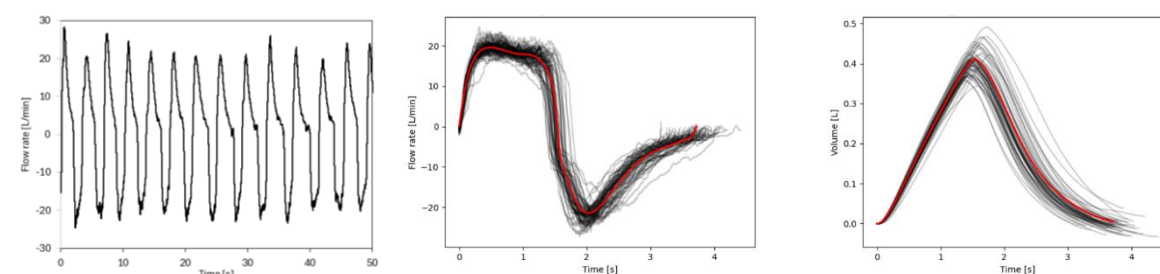


Figure 3: Example of a participant specific breathing pattern. Left: Flow rate measurement. Mid: Individual (black) and phase averaged (red) flow rate. Right: Individual (black) and phase averaged (red) tidal volume

Data were analysed using Statgraphics Centurion XVII. A ANOVA assessed the effects of age, nebulizer variant, gender, and health status on the breathing pattern parameters.

Results

The main results of the ANOVA are shown in Figure 4:

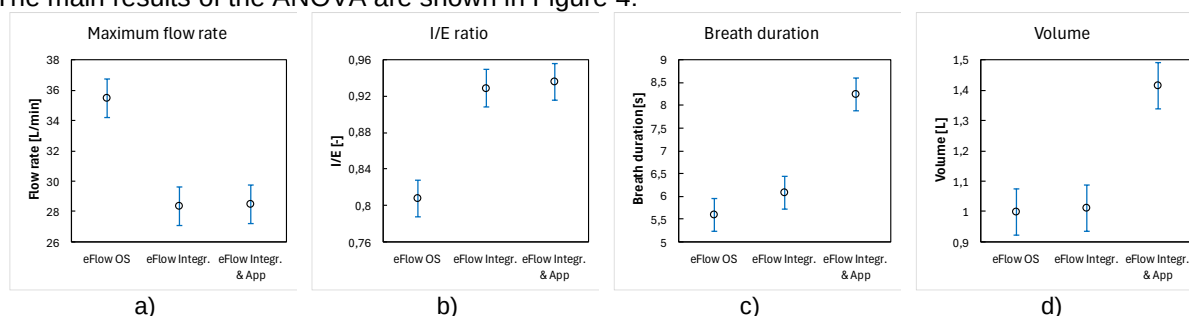


Figure 4: Mean values of all participants and 95 % LSD intervals. a) Maximum flow rate, b) I/E-ratio, c) Breath duration, d) Tidal volume

Maximum inspiratory flow: Average maximum flow rate was around 30 L/min across all groups. Gender, age and intervention showed significant effects on this parameter. The eFlow OS was associated with significantly higher peak flow (35.5 L/min) than eFlow Integrated (28.4 L/min) or eFlow Integrated & App (28.5 L/min).

I/E ratio: The mean value was 0.94 for the healthy group, 0.85 for the obstructive and 0.88 for the restrictive group. All four factors showed significant effects. The eFlow OS (0.81) differed significantly ($p < 0.05$) from eFlow Integrated (0.93) and eFlow Integrated & App (0.94), while the latter two did not differ significantly.

Breath duration: Nebulizer variant, gender and age showed a significant effect on breath duration. Within the nebulizer variants, mean breath duration with App (8.25 s) was significantly longer than without (eFlow OS: 5.59 s, eFlow Integrated 6.09 s).

Tidal volume: The mean tidal volume was 1.23 L for the healthy group, 1.07 L for the obstructive group and 1.05 L for the restrictive group. The effects of age, nebulizer variant and gender on tidal volume were highly significant ($p < 0.01$), while the effect of health status did not reach significance ($p = 0.25$). App use had a significant effect on tidal volume (1.4 L) and was significantly different ($p < 0.05$) from the other nebulizer variants (~ 1.0 L).

To extract the impact of the nebulizer variant on the participants' breathing, the median averaged breathing patterns of all participants were median averaged again for each nebulizer variant. Since the breathing of the three participant groups differed strongly, this analysis was done separately for each group (Figure 5).

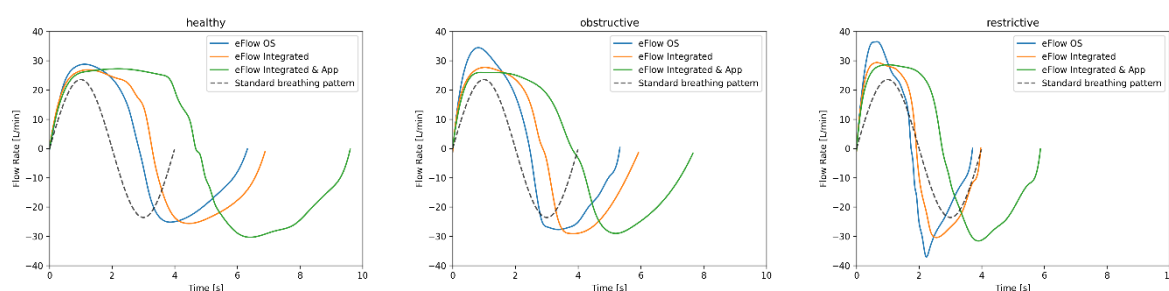


Figure 5: Median averaged, device specific breathing patterns for the three participant groups

For all participant groups, eFlow Integrated prolonged the breath duration and reduced maximum flow rate, especially if the app is used additionally. It becomes also apparent that the breath duration decreases from healthy to obstructive to restrictive participants, while the maximum flow rate increases in this order. While the breathing pattern of restrictive patients is somewhat close to the standard USP breathing pattern (sinusoidal, tidal volume 500 ml, Inspiration 2 s, Expiration 2 s), there is a large deviation for the other participant groups. The aforementioned changes in breathing pattern were to a large extent achieved by the built-in direction-dependent resistance integrated into the nebulizer. Questionnaire analysis showed that this resistance was well tolerated.

Discussion & Conclusion

The conducted investigation showed that breath-guiding within a nebulizer can significantly alter the breathing pattern of healthy and diseased probands. The guiding implemented in the eFlow Integrated effectively lowers maximum flow rates by around 20 % through all participant groups to the target value of below 30 L/min compared to the reference eFlow OS. This was achieved by a well-tolerated built-in

resistance which is known to foster slow flow rates and visual and haptic feedback. Slower flow rates lead to less drug loss in the upper airways and therefore enhanced drug deposition in the lungs [4] [10]. The guiding also positively influences the I/E ratio towards a longer inspiration phase by more than 15 % for the eFlow Integrated. Longer inspiration phases allow for longer aerosol production times in breath-triggered devices contributing directly to short nebulization times [1]. The app with guiding towards deep and long inhalation and visualization could significantly increase the tidal volume by approximately 40 % compared to the other nebulizer variants. With higher tidal volumes a greater proportion of particles enters the lower airways. At the same time, the usage of the app also increased the breath duration by 47 % resulting in increased sedimentation and hence deposition. The above-mentioned improvements therefore show the potential to optimise drug delivery, supporting positive therapy outcomes. Errors in inhalation technique and handling are common, compromising the therapeutic success of inhalation therapy. This stresses the need for training and education on proper inhalation technique, which is often limited by time and resource constraints in daily practice and might lead to reduced real-world effectiveness compared to clinical trial settings [5]. The breath-guiding of the eFlow Integrated as well as the optional app may serve as an education tool to reduce the burden on health care professionals and facilitate correct inhalation technique.

The conducted investigation depicts real-world breathing patterns of patients with obstructive and restrictive lung diseases as well as healthy subjects during inhalation. A strong deviation between these and the standard USP breathing pattern (Figure 5) was found which has also been observed by Mišík et al. [6] and should be considered when testing nebulizers. In contrast to previous publications that focused on individual participant cases or small cohorts of healthy participants [6] [7] [8], this investigation was systematically designed and includes a representative sample of healthy subjects and patients with both obstructive and restrictive lung diseases, strengthening the validity and generalizability of the findings. This dataset provides a solid foundation for future investigations and may serve as a reference point for subsequent research in the field. However, certain limitations had to be accepted in the investigation. As a result of the limited number of participants with lung diseases available, randomization in the order of nebulizer variants was not possible. Hence a certain training effect might affect the data. Moreover, the three groups differed significantly in age, height, and gender. Because height and weight were related to age, only age and gender was included in the ANOVA to account for these systematic differences in the participant groups. Adding age as a factor into the ANOVA greatly improved the accuracy of the models and outweighed the effect of health status and other factors on all parameters. Interestingly, age appears to be the strongest predictor for the tested breathing parameters. The existing dataset is currently being augmented with deposition data derived from simulations, providing insight into the distribution of drug deposition and the duration of treatment.

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